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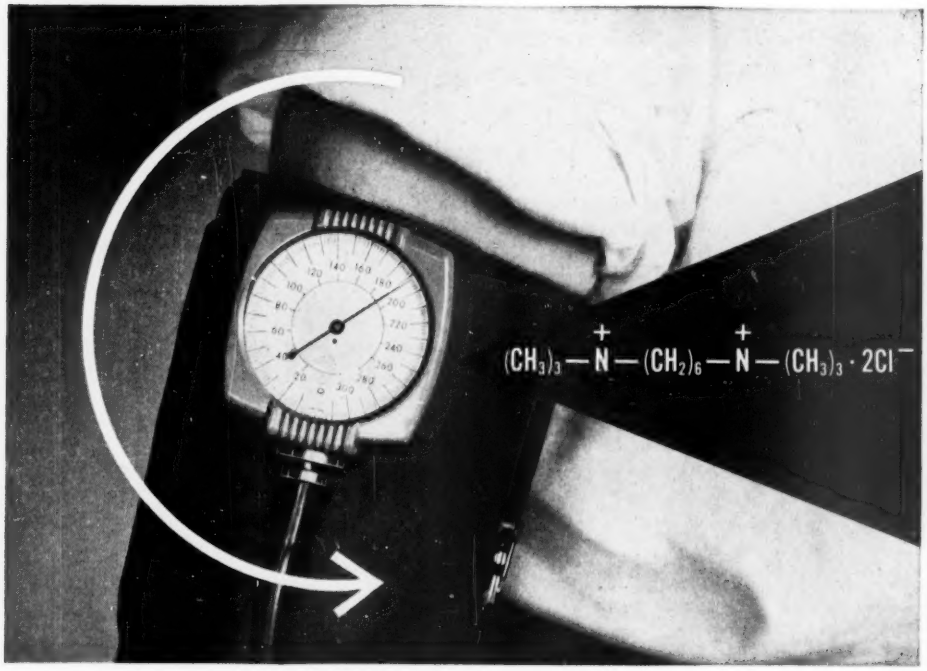

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1. Grimson, K. S., et al.: J.A.M.A. *149*:215 (May 17) 1952.

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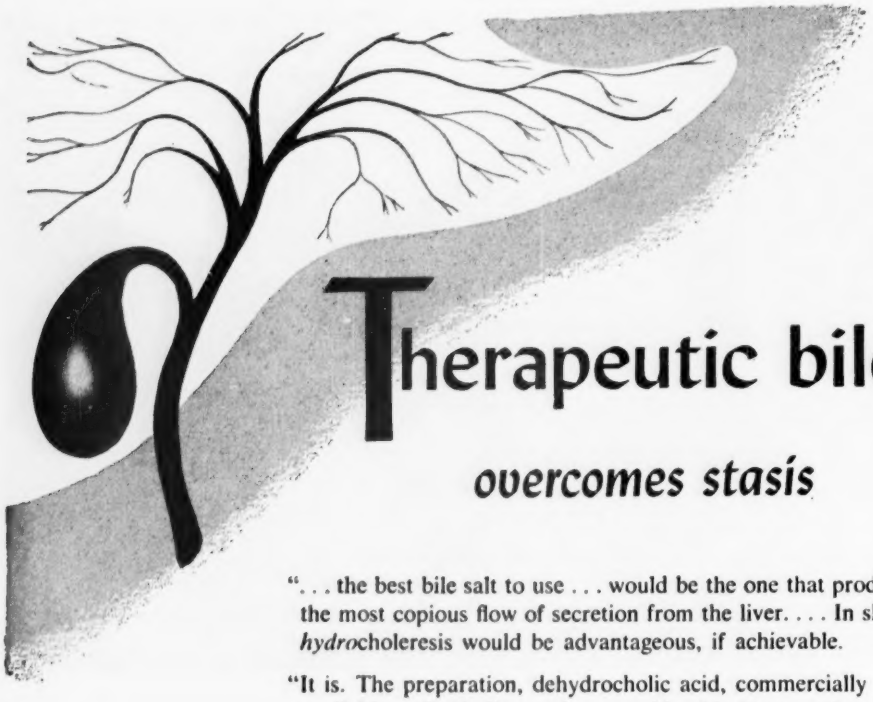

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*Beckman, H.: Pharmacology in Clinical Practice, Philadelphia, W. B. Saunders Company, 1952, p. 361.

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2. Furlong, J. H.: Delaware State M. J. 24:170, 1952.

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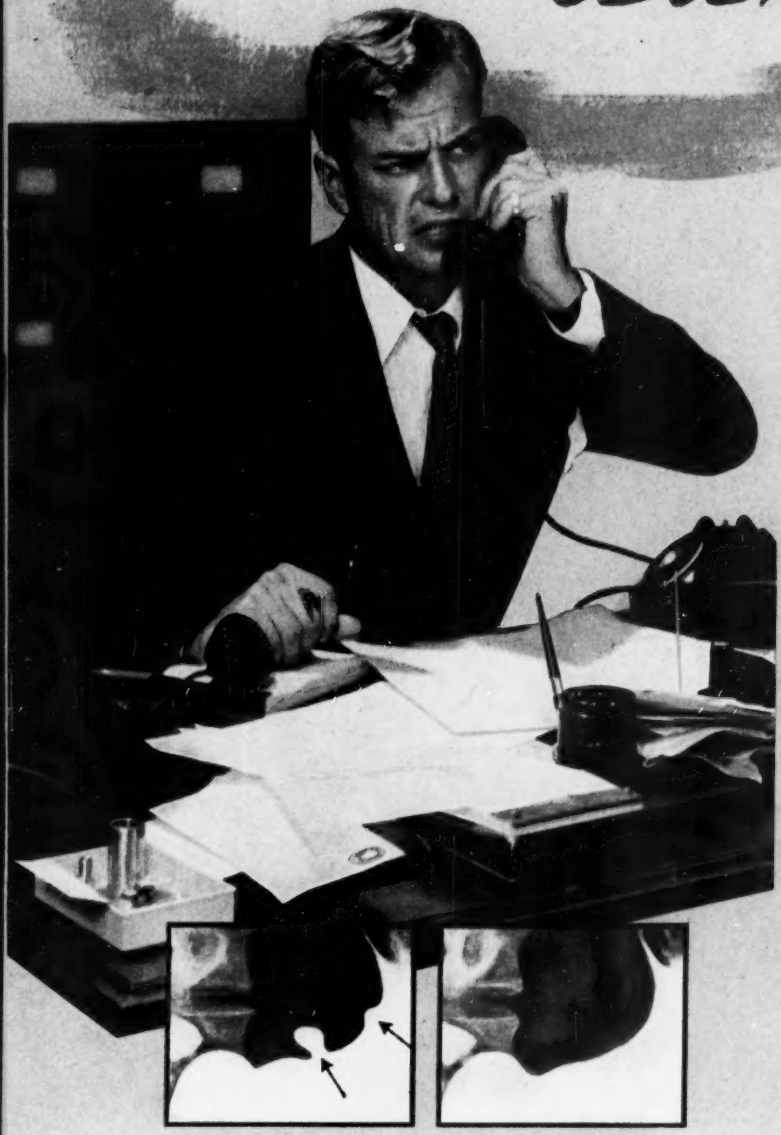

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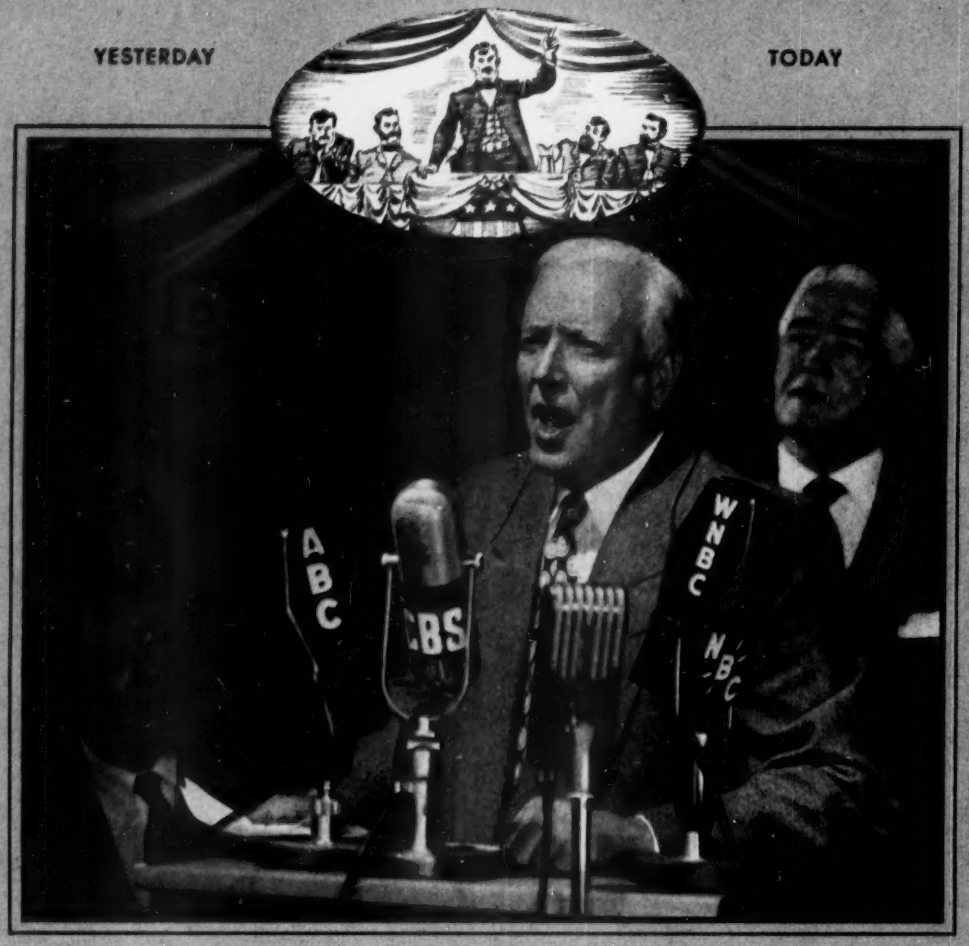

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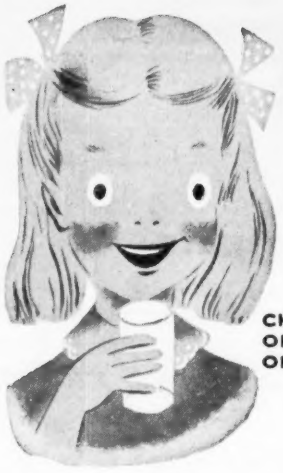

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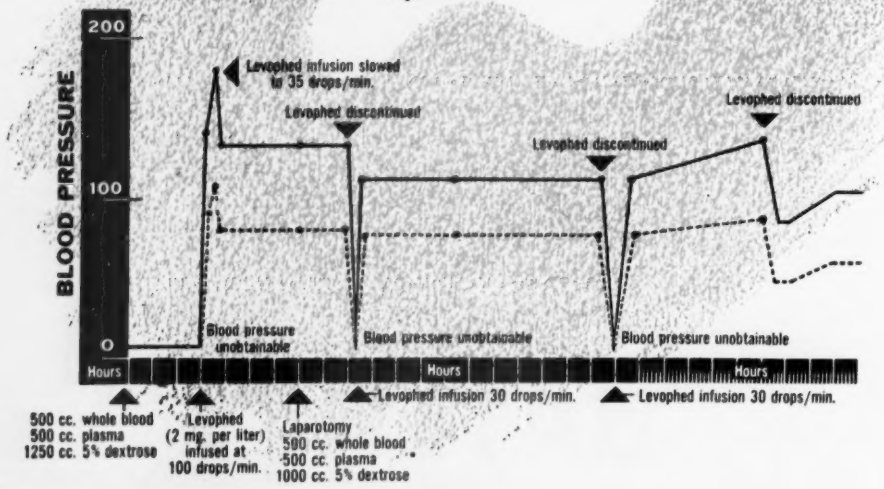

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Volume 248 MARCH 12, 1953 Number 11

CANCER OF THE LUNG IN PHYSICIANS*

ERNEST L. WYNDER, M.D.,† AND JEROME CORNFIELD, B.S.‡

NEW YORK CITY AND BETHESDA, MARYLAND

DURING the past two years, nine separate investigations have presented evidence that tobacco smoking is associated with the development of bronchiogenic carcinoma.[1-9] Studies by Wynder and Graham[2] and Doll and Hill,[7] both based on personal interviews with over 600 patients with cancer of the lung, in particular were in close agreement quantitatively as well as qualitatively. Data on the possible relation of industrial exposures to cancer of the lung showed that although there is some evidence of a greater than average risk in some occupations, these occupations could not account for the general increase in pulmonary cancer.[10]

In line with these studies, it was thought of interest to select a particular population group, homogeneous economically, with little occupational exposure to respiratory irritants and with equal access to diagnostic facilities. Physicians were believed to represent such a group. The present study is a report on the exposure to tobacco and other possible respiratory irritants of 63 physicians with cancer of the lung, and 133 physicians with cancer in areas where respiratory irritants are not believed to play a part.

METHODS OF STUDY

The death notices in the *Journal of the American Medical Association* served as the source of information for the primary diagnosis. The years 1950 and 1951 and the first two months of 1952 were selected, and for the patients with cancer of the lung, 1949 death notices were used in addition. The addresses of physicians were obtained from the *American Medical Directory*. Letters were sent to the estates of physicians who had died from cancer of the lung, colon, stomach, kidney and bladder, leukemia, lymphoma and sarcoma. No follow-up letters were sent.

The letter and questionnaire read as follows:

We are undertaking a study concerning the possible effects of external irritation on the development of various types of cancers in physicians. The particular cases that we are contacting have been obtained from the death notices of the *Journal of the American Medical Association*. It goes without saying that in the final analysis of this survey, no individual names of the deceased will be used.

We should appreciate very much if the enclosed questionnaire could be answered by someone most familiar with the deceased during his adult life.

The results of this study may throw considerable light on the preventive aspects of some types of cancers. Your co-operation in this matter may thus be of the greatest importance in furthering our knowledge about cancer.

Name .....Age .....Cancer .....

1. Did he ever smoke? Yes..... No.....
2. At what age did he begin to smoke? ..... At what age did he stop smoking? .....
3. How much tobacco did he average per day during the past 20 years of his smoking? Cigarettes ..... Cigars ..... Pipes .....
4. Did he hold any jobs outside of his medical practice and did he have any hobbies where he had been exposed to dusts and fumes?
   In particular, has he used insecticide sprays excessively?
   If so, when and for how long?
   Yes ..... No ..... Years: From ..... to ..... Type of job .....
5. Relationship of person completing this questionnaire .....
   Length of time of personal acquaintance with the deceased.....
   If unable to answer the questions, please state reason .....

Of the 118 letters sent to physicians who had died of pulmonary cancer 11 were returned unopened because address was unknown; of those delivered, 63 were completed and returned. Of the 214 letters sent to physicians who had died of other forms of cancer 6 were returned with address unknown; of those delivered, 133 were completed and returned. Thus, 58.9 per cent of the letters to patients with cancer of the lung and 63.9 per cent of the controls delivered were returned.

RESULTS

Age Distribution

The distribution by age at death in the cases of cancer of the lung and in the control group is shown in Table 1. The results are in agreement with previous data, as recently presented by Korteweg,[11] showing that the average age at death is lower for

*From the Department of Medicine, Georgetown University Hospital, Washington, D. C., the Department of Medicine, Memorial Center for Cancer and Allied Diseases, New York City, and the Biometrics Section, National Cancer Institute, Bethesda, Maryland.

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‡Statistician, National Institutes of Health, United States Public Health Service; adjunct professor of statistics, American University, Washington, D. C.

patients with cancer of the lung than for those with other forms of cancer.

Amount of Tobacco Used

The distribution by amount smoked is shown in Table 2 for both groups. The differences are quite marked. A fifth of the control group were essentially nonsmokers,—that is, they smoked the equivalent of less than 1 cigarette a day,—whereas only one twenty-fifth of the patients with cancer of the lung smoked this little. Similarly, a third of the physicians with pulmonary cancer smoked more than 35 cigarettes a day, and only an eighth of the control group smoked this much. These differences are statistically significant: chi-square is computed from the original frequencies with 5 degrees of freedom as 36.0, $P<0.01$.

TABLE 1. *Age Distribution of 63 Physicians with Cancer of the Lung and 133 Physicians with Cancer outside the Respiratory Tract.*

AGE AT DEATH	PATIENTS WITH PULMONARY CANCER		CONTROL GROUP	
	NO.	PER-CENTAGE	NO.	PER-CENTAGE
yr.				
30-39	0	0.0	6	4.5
40-49	7	9.3	13	9.7
50-59	12	20.9	19	14.2
60-69	27	43.5	28	21.0
Over 70	17	25.8	67	50.3
Totals	63		133	

As a check, we have broken the control group into three independent groups, with approximately equal numbers of cases. It will be seen that no matter which of the three control groups is used, the conclusion that patients with cancer of the lung smoked considerably more than the controls is unaffected. The variations among the three control groups are not statistically significant (chi-square = 16.39, d.f. = 10, $p>0.05$).

Estimation of Mortality Rates

The results of this comparison are sufficient to demonstrate how many more smokers are found among patients with pulmonary cancer. They do not show by themselves how many more patients with cancer of the lung are found among the smokers. Thus, the over-all annual mortality from cancer of the lung and bronchus among male physicians forty to eighty years of age is approximately 50 per 100,000.*[12] What is this rate for nonsmokers and for moderate and very heavy smokers, and how does it compare with similar rates among the general population in this country and abroad?

It seems evident that if more smokers are found among patients with cancer of the lung than among the controls, more cases of pulmonary cancer will be found among the smokers than among the nonsmokers. In fact, as Cornfield[13] has shown, if the annual mortality rate from lung cancer among physicians is 50 per 100,000, the data in Table 2 imply that the rate per 100,000 among nonsmokers is $\frac{4.1}{20.6} \times 50$, or 10 per 100,000. We have accordingly converted the data of Table 2 to the rates shown in Table 3.† For comparative purposes, we have made the same conversion for the results of the general population of Wynder and Graham.[2] The results of the two studies are in good agreement, the rates rising from 10 per 100,000 for nonsmokers to 133 per 100,000 for the heaviest smokers, whereas the same rates estimated for the general population rise from 4 to 134 per 100,000. In Figure 1 we have plotted these data as well as estimates based on the recent study in the United Kingdom by Doll and Hill,[7] expressing the mortality rates as a percentage of the general average. The two curves for the United States are somewhat steeper than that for

TABLE 2. *Distribution According to Amount Smoked.**

AMOUNT SMOKED†	LUNG CANCER (63 CASES)	CONTROL GROUP			
		TOTAL (133 CASES)	STOMACH AND KIDNEY (43 CASES)	COLON AND LYMPHOMA (45 CASES)	BLADDER, LEUKEMIA AND SARCOMA (45 CASES)
	%	%	%	%	%
Less than 1	4.1	20.6	25.7	24.8	11.6
1-9	0.0	13.1	4.1	14.1	18.9
10-14	1.7	9.7	1.4	9.5	19.0
15-20	26.6	27.3	27.8	24.1	25.7
21-34	33.8	16.6	16.9	13.1	20.7
35 or more	33.8	12.7	24.2	14.4	4.1

*The data are standardized for age. The standard population used for each age group is the harmonic mean of the lung-cancer and control population. One cigar has been arbitrarily treated as the equivalent of 5 cigarettes, and 1 pipeful as 2½ cigarettes.

†Equivalent number of cigarettes per day.

*The rate for all white males in this age group in 1949 was somewhat over 50 per 100,000, whereas the most recent study of mortality among physicians, covering the years 1938-1942, showed that the ratio for all respiratory cancer (physicians to all white males) was 0.90. Since this estimate was apparently based on 150-175 actual deaths from respiratory cancer, the ratio is actually not significantly different from unity.

†This calculation depends on the assumption that the control group of doctors is representative of all doctors so far as smoking habits are concerned, age group by age group. This assumption may not strictly be true. As a test, mortality may be calculated by means of each of the three control groups of Table 2 in turn. Using the first control group, we estimate mortality of nonsmokers as 8 per 100,000, using the second as 8 per 100,000, using the third as 18 per 100,000. Similarly, for the group smoking 35 or more equivalent cigarettes, the rates using the three control groups are 70, 117 and 412 per 100,000. Clearly the increases from 8 to 70, from 8 to 117 and from 18 to 412 all show pronounced associations between amount smoked and development of pulmonary cancer.

the United Kingdom, but, except for this, the agreement among all three is quite good.

Type of Tobacco Smoked

In the previous tables all forms of smoking have been combined. Table 4 shows the results for different types of smokers and compares them with similar results for the general population. Again, there is close agreement, both studies showing mortality higher among cigarette smokers than among either pipe or cigar smokers.

TABLE 3. *Estimated Annual Mortality Rates per 100,000 from Cancer of the Lung among Different Groups.*

AMOUNT SMOKED*	PHYSICIANS	GENERAL MALE POPULATION (U. S.)†
Less than 1	10	4
1–9	0	10
10–14	9	27
15–20	49	49
21–34	102	134
35 or more	133	134

*Equivalent number of cigarettes per day.

†Estimated from results given in Wynder and Graham,[3] assuming an annual mortality of 50 per 100,000.

Other Possible Respiratory Irritants

Exposure to other possible respiratory irritants among physicians might occur in some hobbies, in work before beginning medical practice or because of urban living; 14.3 per cent of the patients with pulmonary cancer were exposed to possible respiratory irritants in work or hobbies. Exposure in hobbies included exposure to insecticides (7.9 per cent), and 1 patient each to paint and sawdust; 1 physician had been gassed during the war, and 1 had been exposed to steel dust before beginning medical practice. Among the control group, 10.4 per cent had been exposed to possible respiratory irritants. These included 6.1 per cent exposed to insecticides, 2 to sawdust and 1 each to paint and metal dust in their hobbies, and 1 physician each had been exposed to machine dust and stone dust before entering the practice of medicine. The differences between the patients with cancer of the lung and the control groups are not statistically significant.

The urban-rural distribution was calculated from the home addresses of the physicians. Among the patients with pulmonary cancer 49.6 per cent lived in towns with a population of less than 50,000, compared with 58.8 per cent in the control group, whereas 23.3 and 19.0 per cent, respectively, lived in cities with a population of more than 500,000. These differences are also not statistically significant.

TABLE 4. *Present Distribution of Lung-Cancer and Control Groups by Type of Smoking Used, with Estimated Mortality per 100,000 Cases of Pulmonary Cancer among Physicians and among the General Population.*

TYPE OF SMOKER	DISTRIBUTION AMONG PATIENTS WITH PULMONARY CANCER	DISTRIBUTION AMONG CONTROLS	ESTIMATED ANNUAL MORTALITY PER 100,000	
			AMONG PHYSICIANS*	AMONG GENERAL POPULATION†
	%	%		
Nonsmoker	4.1	20.6	10	4
Smoker: Total	95.9	79.4	60	58
Predominantly:				
Pipe	6.1	7.7	40	16
Cigar	13.0	26.6	24	22
Cigarette	76.8	45.2	84	70

*$\frac{\text{Data in column 2}}{\text{Data in column 3}} \times 50$.

†Based on Wynder and Graham.[3]

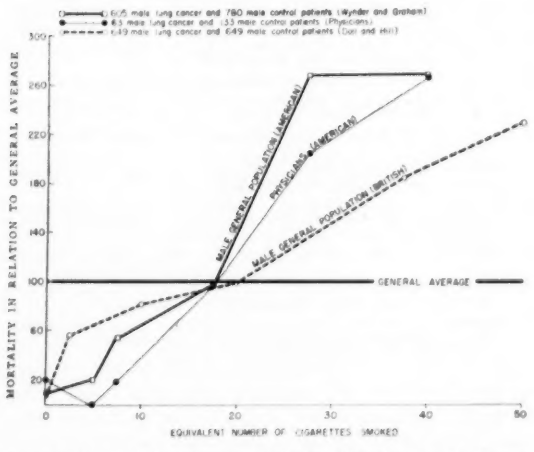

FIGURE 1. *Relation between Relative Mortality and Amount Smoked, Data of the Present Study Being Compared with Those of Doll and Hill[1] and Wynder and Graham.[3]*

DISCUSSION

The method of data collection used in this study differed from that of our previous study, which was based on personal interviews.[2] The present results are based upon recollection by the patient's immediate family about the patient's habits. The response of the physicians' families was as high as could be expected for this type of questionnaire request. A 40 per cent nonresponse rate introduces some uncertainty that cannot be objectively appraised. It is of interest, however, that the proportion of questionnaires returned did not differ appreciably between the patients with cancer of the lung and the controls. Any possible errors of judgment on the part of the families should have been approximately equal in the two groups, and may thus be reasonably expected to balance one another.

Histologic diagnosis of the cancer has not been obtained. The significance of such a diagnosis has previously been stressed,[2] it being pointed out that exogenous irritants played the greatest role in the

epidermoid and undifferentiated lung cancer with a much lesser (if in fact any) role in the production of adenocarcinoma. On the basis of general statistics, we may assume that over 90 per cent of the cases represented epidermoid or undifferentiated cancer of the lung.[2] The histologic diagnosis in the 2 patients who were nonsmokers is not available.

This survey was designed to give contributory data for either confirming or denying the evidence presented in the base line survey, through the use of a different approach and through the selection of a special population group. As such, the study is in close agreement with previous investigations in that it shows that patients with cancer of the lung smoke much more heavily than those with other types of cancers, of the same age and economic group; in turn, there is a considerably greater number of nonsmokers and light smokers among the control than the patients with cancer of the lung.

As we had previously found, cigarette smoking was more common in the patients with pulmonary cancer than in the controls. However, 13 per cent of the former were predominantly cigar smokers. The mortality rate is greatest among cigarette smokers, but even among cigar and pipe smokers it is greater than that among nonsmokers, indicating an association of cancer and smoking to all three forms of smoking, even though this relation appears greatest with cigarette smoking. The role of inhaling of tobacco smoke, which we have previously stressed to be of probable importance in cancer of the lung, was not studied in this survey.

The closeness of the results of this survey with the more extensive ones of Wynder and Graham[2] and Doll and Hill[7] stands out. These data indicate that results will be similar if the method of collecting the data has been similar and adequate. The importance of getting personal data in this regard is obvious. The close results of these separate investigations underline evidence that there is a close association between tobacco and cancer of the lung.

The exposure to respiratory irritants other than tobacco was not significantly different in the two groups. Previous data have presented some suggestive but statistically inconclusive evidence that exposures to paint, metal dust, wood dust and some insecticides may be of some importance in the etiology of primary cancer of the lung. The data on the urban-rural distribution of cancer of the lung and control cases do not incriminate city life as an important factor, since they show a roughly similar rural-urban distribution for the two groups.

Summary and Conclusions

Exposures to possible respiratory irritants were studied in 63 physicians with cancer of the lung and 133 physicians with cancer outside the respiratory tract. A highly significant association between the use of tobacco and the development of pulmonary cancer was found among physicians.

The estimated mortality from cancer of the lung rose from 10 per 100,000 among nonsmoking physicians to 133 per 100,000 among physicians smoking 35 or more cigarettes a day.

There were no significant differences in exposure to respiratory irritants other than tobacco among the two groups.

These results agree with those of previous studies.

We are indebted to the families and friends of the physicians included in this study for their co-operation.

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ACUTE POSTOPERATIVE PANCREATITIS*

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ACUTE pancreatitis as a complication of surgical operations on organs adjacent to the pancreas has been recognized for many years. Because it has been regarded generally as a rare occurrence attributable to direct injury to the pancreas or, in operations on the biliary tract, to reflux of bile into the pancreatic duct, the subject has not received adequate attention in the literature. Our attention was drawn to this problem by an experience with 8 cases over a two-year period and by the excellent studies of Millbourn[1] and Warren.[2] The latter author's data are of particular interest because they demonstrate that this highly lethal complication may occur without injury to the pancreas or its blood supply and in situations in which reflux of bile can be excluded.

Although the reported incidence of postoperative pancreatitis seems to be low, less than 50 cases having been described in the literature since 1940, it is likely that it is more common than has been realized. Undoubtedly, many cases are not reported. Moreover, if a complete post-mortem examination is not performed the condition may be interpreted as postoperative peritonitis.

Etiology

The voluminous and controversial literature on acute pancreatitis overshadows the salient facts that have been demonstrated by both pathological and experimental studies. The excellent work of Wangensteen,[3] Dragstedt,[4] Rich,[5] Popper,[6] Lium[7] and others provides what seem to be sufficient data for a rational understanding of the pathogenesis of this disease. Our interpretation of these data is presented somewhat didactically to furnish a background against which our own material may be appraised.

The fundamental factor in the production of acute hemorrhagic pancreatitis is the presence of pancreatic enzymes of a high trypsinogen content in contact with vascular pancreatic tissue. This has the following implications: either the pancreatic ducts are ruptured or the pancreatic secretions have been forced through the wall of the ducts into the interstitial tissues; the pancreas is capable of active secretion; and the site and extent of rupture of the ducts or extravasation is such that the pancreatic secretion is brought into contact with the blood vessels and parenchyma of the gland. It is not essential that the pancreatic secretion be in contact with bile or duodenal juices since it has been shown that trypsinogen can be activated by calcium ions or tissue juices. However, the presence of bile or duodenal contents materially accelerates the pathological sequences. The basic pathological component, however, is an extravasation of necrotizing enzymes into the interstitial tissue of the pancreas.

Table 1. *Anatomic Relations of the Pancreatic and Common Bile Ducts.*

Method of Study	Author	No. of Cases	Common Channel	Reflux Possible	Reflux Demonstrated
			No. of cases	No. of cases	No. of cases
Anatomic dissection	Opie[8]	100	89	28 (28%)	
	Mann[15]	192	62	42 (20%)	
Injection of bile ducts after occlusion of papilla	Millbourn[11]	200			171 (85%)
	Cameron[13]	100			66 (66%)
Cholangiography*	Ivy[10]	1431			503 (35%)

*Collected series.

A reflux of bile into the ducts was originally postulated by Opie,[8] and much of the confusion and controversy about the pathogenesis of this disease stems from his work. The present status of this controversy can be summarized as follows: studies of the anatomic relation of the biliary and pancreatic ducts by injection and dissection technics, by anatomic identification and by cholangiography show that a common channel between the pancreatic and biliary ducts existed in approximately 70 per cent of the cases studied (Table 1). There is considerable disagreement, however, regarding whether or not bile could actually reflux into the pancreatic ducts after contraction of the sphincter of Oddi, since in many cases closure of the sphincter appears to occlude both ducts (Table 1). Assuming there is a common channel that permits reflux, it is doubtful whether the differential secretory pressure between the biliary and pancreatic ducts would favor it since that in the pancreatic ducts exceeds that in the biliary system. Pancreatic enzymes can be found in the common duct with considerable fre-

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quency, but bile in the pancreatic duct has rarely been demonstrated. Moreover, it is fairly well established that bile in itself, without an increased pressure, has no deleterious effect when present in the pancreatic ducts. When all factors have been taken into consideration the evidence indicates that a reflux of bile is not a primary factor in the production of acute pancreatitis.

The significant factor in the pathogenesis of this disease appears to be an obstruction of the pancreatic duct. This may occur in a variety of ways. The duct of Wirsung may be blocked by edema, inflammation, a gallstone or spasm of the sphincter of Oddi. In the cases in which a separate channel for the pancreatic ducts exists occlusion may result from edema and inflammation of the duodenal mucosa. The duct of Santorini may be occluded in the same manner, and if it is draining a significant portion of pancreatic tissue, which it does in about 10 per cent of patients, this may set the stage for pancreatitis. The duct of Santorini is particularly vulnerable to surgical injury during gastric resections for duodenal ulcer since it enters the duodenum on its ventral aspect nearly 2.5 cm. proximal to the entrance of the common bile duct. Finally, the pancreatic ducts may become occluded by detritus, pancreatic calculi, metaplasia of epithelium or sludging of the pancreatic secretions. In these conditions obstruction may involve peripheral portions of the ductal system leaving the main channel of the pancreatic duct intact and apparently normal on gross pathological examination.

Assuming an obstruction of the pancreatic ducts, serious pathological sequences will ensue only if the gland is actively secreting, when rupture of the ducts or extravasation of secretion through the walls of the ducts occurs. The character of the pancreatic secretions is an important variable affecting the extent of the pancreatic inflammation. If the secretion consists largely of water and inorganic constituents (which is the principal action of the hormone secretin), pancreatic edema ensues. The presence of the enzyme lipase leads to fat necrosis. The specific hemorrhagic and necrotizing action of pancreatic secretions depends upon the presence of trypsinogen, which is elaborated through vagal stimulation. Foods, particularly proteins and meat extracts, exert a major secretory effect on the production of pancreatic trypsinogen.

Finally, in addition to the variables mentioned above, there may be a primary vascular factor in acute pancreatitis. Acute infarction of the pancreas, "pancreatic apoplexy," may result in acute hemorrhagic pancreatitis. Popper[6] has shown that the pancreatic edema that follows experimental obstruction of the ducts and stimulation of the gland by secretin will proceed to acute hemorrhagic necrosis if an ischemia of the gland is produced by temporary occlusion of the principal pancreatic artery. Occlusion of the same vessel for the same length of time in normal control animals had no ill effects.

Infection and direct trauma to the gland are additional factors that must be considered. It appears that, if sufficiently extensive, either of these factors may lead to pancreatic necrosis. The adverse effect of infection or trauma, if added to the more common causes, is obvious.

When one considers the many variables that affect the pathological sequences in acute pancreatitis, it is not difficult to see why what appears to be the same clinical factors result in 1 case in acute hemorrhagic necrosis and in another in pancreatic edema, or at times in no significant abnormality. With these variables in mind, the following cases of postoperative pancreatitis are considered.

Case Reports

Case 1. V. F. (P.B.B.H. 9C173), a 30-year-old single man, entered the hospital because of abdominal pain of 36 hours' duration. His illness was characterized by severe epigastric pain of sudden onset associated with soreness between the shoulder blades, jaundice, dark urine and light stools.

Physical examination revealed an obese, florid, heavy-set man in good general condition. The positive findings consisted of icterus and tenderness and spasm in the epigastrium and right upper quadrant of the abdomen.

Examination of the blood showed a hematocrit of 45 and a white-cell count of 13,600. The serum bilirubin was 7.4 mg., the thymol turbidity 20 units (normal range, 8 to 40 units), and the serum amylase 32 units per 100 cc. (normal, up to 180 units). The urine was normal except for the presence of bile.

Plain x-ray films of the abdomen and chest disclosed no abnormality.

Although the patient was afebrile on admission, he was given supportive therapy, including penicillin. Operation was performed 36 hours after admission. Exploration of the abdomen disclosed a thick-walled, inflamed gall bladder. Sludge was encountered in the common bile duct, and a stone was impacted at the ampulla of Vater. The pancreas was normal to palpation. Cholecystectomy and exploration of the common duct were completed, but to remove the stone from the ampulla of Vater a duodenotomy and sphincterotomy were necessary. The common duct was drained by means of a long-arm T tube, which was passed into the duodenum.

The postoperative course was characterized by acute gastric dilatation and profound peripheral collapse occurring about 24 hours after operation. Despite infusions of dextrose and water, plasma and blood, the blood pressure responded poorly. The temperature rose on the day after operation to 105°F., and the patient became oliguric. Laboratory studies within 48 hours of operation disclosed a blood urea nitrogen of 56 mg., bilirubin of 4.6 mg., and serum amylase of 610 units per 100 cc. The patient remained oliguric and disoriented. There was a profuse drainage of dark, bloody material from the drain. Distention and signs of generalized peritonitis followed, and he died on the 5th postoperative day.

At post-mortem examination there was an acute hemorrhagic pancreatitis with retroperitoneal hemorrhage and fat necrosis throughout the peritoneum and retroperitoneal tissues and extending well up into the left side of the chest behind the pleural reflection. The duodenum and biliary passages were not abnormal. There was a separate entrance of the common duct and duct of Wirsung into the duodenum. The pancreas itself was totally necrotic, but the pancreatic duct was found to be patent. Microscopical examination of the pancreas disclosed extensive necrosis, with diffuse polymorphonuclear-cell infiltration. There were rare foci of squamous metaplasia in the ducts.

It is difficult to explain why such severe pancreatic necrosis followed this operation. Reflux of bile into the pancreas was impossible since there

was a separate opening of the common duct and the duct of Wirsung. A major obstruction to the pancreatic duct could not be demonstrated at postmortem examination. The sole factors, therefore, appear to have been manipulation of the pancreas, mobilization of the head of the pancreas and local trauma incident to the disimpaction of a stone. The frequency with which this procedure may be done without untoward sequelae is so high that one questions whether in itself it is sufficient to account for the extensive pancreatic lesion.

Case 2. L. V. (P.B.B.H. 8B216), a 56-year-old woman, entered the hospital because of renal failure after a cholecystectomy and common-duct exploration performed 3 days previously in another hospital. Although obese, the patient was regarded as a good risk for operation, which had been performed without difficulty. Three stones were encountered in the common bile duct. These were removed and the sphincter of Oddi was moderately dilated. No abnormalities of the liver or pancreas were noted. The pancreas was mobilized to facilitate palpation of the lower end of the common duct and the removal of the calculi. The course was remarkably similar to that in the preceding case in that severe gastric dilatation and peripheral collapse occurred about 24 hours after operation. The blood pressure failed to respond to fluids given intravenously. Blood was not employed. On the 2d day after operation jaundice became pronounced, and there was oliguria and azotemia.

Physical examination showed a drowsy patient, who seemed in moderately good condition. There was little evidence of generalized peritonitis. The T tube was draining bile effectively, and there was only moderate serous drainage from the cigarette drain. Because little urine was passed and there was a progressive rise in the blood urea nitrogen, dialysis on the artificial kidney was carried out on the 5th day after admission (7 days after operation). The initial response to dialysis was favorable. The patient's general condition seemed somewhat improved, and shortly thereafter she began to pass moderate amounts of dilute urine. Laboratory studies, however, disclosed persistent azotemia, a progressive elevation of the serum bilirubin and a marked leukocytosis. A biliary fistula developed around the T tube. The patient became disoriented and became feverish (maximum temperature of 103°F.). On the 12th day after operation she went into profound peripheral collapse and remained hypotensive despite vigorous fluid and colloid replacements. A serum amylase on the day of death was 200 units per 100 cc.

Post-mortem examination disclosed an acute hemorrhagic pancreatitis with extensive necrosis, abscess formation and autolysis of the pancreas. A thin rim of mushy necrotic pancreatic tissue surrounded the pancreatic duct, which had a common opening with the common bile duct. The ampulla of Vater was minute, barely permitting the passage of a small probe. The lesser peritoneal cavity was involved in a purulent infection. Microscopical examination of the pancreas disclosed extensive thrombosis of major vessels and considerable interstitial hemorrhage. There was leukocytic infiltration and tubular degeneration of the kidneys.

A functional obstruction of the ampulla of Vater seems to have been a significant factor in this case. The dilatation of the sphincter may have produced local edema and swelling so that the ampulla was occluded postoperatively. The T tube was ineffective, and a biliary fistula developed. Obstruction to the pancreatic duct, possibly aggravated by the forcible dilatation of the sphincter of Oddi, is a logical assumption. The extensive autolysis of the pancreas and the widespread vascular thrombosis and hemorrhage in the pancreas are consistent with a pancreatic secretion rich in trypsinogen. Mobilization of the head of the pancreas may have added a factor of trauma and local ischemia.

Case 3. W. R. (P.B.B.H. 8B725), a 43-year-old man, was admitted to the hospital 7 days after a gastric resection performed in another hospital. He had been in excellent general condition, and a 50 per cent subtotal gastrectomy and vagotomy for duodenal ulcer had been performed by a competent surgeon. There was no unusual trauma to the pancreas during the operation, but the duodenum and pancreas were mobilized to permit adequate closure of the duodenal stump. The duodenal ulcer was excised, and a generous portion of the duodenum was mobilized, freed and inverted so as to permit a satisfactory closure of the duodenum.

The patient did poorly from the 1st day of operation. There was evidence of some mental confusion, high fever and drainage of copious amounts of bile and gastric contents through an inlying gastric-suction tube. The temperature rose to 104°F., and moderate abdominal distention developed. Laboratory studies revealed a progressive elevation of the nonprotein-nitrogen, the maximum value being 165 mg. per 100 cc. The serum amylase was normal. Because of increasing evidence of an inflammatory process in the right upper quadrant of the abdomen, which was manifested by increasing spasm and tenderness in that area, slight progression of the abdominal distention and progressively rising pulse rate, the patient was re-explored. There was no evidence of leakage from the duodenal stump, and a general exploration of the abdomen was not carried out. He was transferred to this hospital within 24 hours of the 2d operation.

On admission he appeared severely ill. He was disoriented, with a pulse rate of 120 per minute, a temperature of 103°F. and respirations of 30 per minute. The abdomen was distended, and there was shifting dullness and diffuse tenderness, with diminished peristaltic sounds. Laboratory studies then disclosed an elevation of the blood urea nitrogen to 105 mg. per 100 cc. The serum amylase was normal; the bilirubin was 3 mg. per 100 cc., and the hematocrit 28 indicating considerable loss of blood. The white-cell count was 30,000. During the next 5 days the patient was treated with supportive measures, consisting of antibiotics, continuous gastric suction and fluid replacement by the parenteral route. He gradually lost ground, however, and on the 5th day after admission (12 days after the initial operation) he was again explored and an acute diffuse, hemorrhagic pancreatitis was found. Over 200 cc. of bloody fluid was removed from the peritoneal cavity. Widespread drainage was instituted, but there was no significant improvement in the patient's condition. For the next 6 days he presented a picture of steadily progressive, overwhelming peritoneal infection and generalized toxicity.

At post-mortem examination there was evidence of generalized peritonitis with fat necrosis. The head of the pancreas was markedly necrotic, with extensive retroperitoneal fat necrosis. There was a left subphrenic abscess, bilateral pleural effusion, a fibrinous pericarditis and markedly enlarged, swollen kidneys. The duodenal stump and the gastrojejunal anastomosis were well healed. Dissection of the blood supply of the pancreas disclosed a ligature around the posterosuperior pancreaticoduodenal artery, which ran anterior to the common bile duct and in the lateral edge of the peritoneal reflection. It had undoubtedly been divided in the course of mobilization of the duodenum. No obstruction to the common bile duct or the pancreatic duct was demonstrable grossly, but the relation of these 2 ducts was not determined at their point of entrance into the duodenum.

Unfortunately, the autopsy material in this case does not exclude the possibility of a separate opening of the duct of Santorini of sufficient size to have been a significant factor in the development of pancreatitis. Ligation of the posterosuperior pancreaticoduodenal artery in itself would probably be of no significance, but if combined with obstruction of the duct of Santorini, it might be a crucial factor in the development of pancreatitis. The inflammatory process and the necrosis in this case were largely

limited to the head of the pancreas and, therefore, were consistent with a vascular component of comparatively limited scope.

CASE 4. C. T. (P.B.B.H. R2641), a 68-year-old man, entered the hospital for therapy of a chronic duodenal ulcer. Physical examination and laboratory data before operation were not abnormal.

At operation it was found that the ulcer was adherent to the pancreas, and there was considerable trauma to the head of the pancreas at the time of mobilization of the duodenum. The ulcer was excised, and a subtotal gastrectomy performed. The postoperative course was complicated by abdominal tenderness and a temperature rise to 103°F. on the 2d postoperative day. The serum amylase was within normal limits. The white-cell count was 17,000. Because of progressive tenderness in the right upper quadrant of the abdomen and the fear of leakage from the duodenal stump, re-exploration was performed on the 3rd postoperative day, and an edematous pancreatitis limited to the head of the pancreas was found. The duodenal stump was intact. The postoperative course from this point on was uncomplicated.

The diagnosis of pancreatitis was established in this case by re-exploration of the abdomen. There was comparatively little fat necrosis and no evidence of extensive hemorrhage or generalized necrosis. This appears to have been a case of pure traumatic pancreatitis, relatively mild in extent and probably not associated with an element of ductal obstruction or vascular damage. One might assume that if the posterosuperior pancreatic vessel had been divided, a sequence of events similar to that in Case 3 might have resulted.

CASE 5. J. A. (N.E.D.H. 32180), a 67-year-old man, entered the hospital for treatment of a carcinoma of the stomach. He was regarded as a good preoperative risk. At operation a subtotal gastrectomy was performed, and a portion of the body of the pancreas was excised because of adherence of the tumor to the surface of the pancreas.

The postoperative course was complicated by severe pain in the upper part of the abdomen and a rapid pulse. The temperature remained normal for several days, but the serum amylase was 548 units per 100 cc. The patient's condition progressively deteriorated, with signs of peritoneal fluid and abdominal distention; he became dyspneic and disoriented and appeared gravely ill. On the 7th day after operation, because there seemed to be a marked degree of ascites, abdominal paracentesis was attempted. A loop of bowel was perforated by this procedure, and an immediate laparotomy was therefore performed. At operation the perforated loop of bowel was sutured, and a limited exploration disclosed bloody fluid within the peritoneal cavity and evidence of fat necrosis. After operation the patient was given massive doses of penicillin and streptomycin and 3 x-ray treatments to the pancreas. Over the course of the next 11 days he failed progressively, with increasing jaundice and toxemia.

Post-mortem examination showed extensive fat necrosis, with an organizing fibrinous peritonitis. A major branch of the pancreaticoduodenal artery was occluded by thrombosis. There was bilateral bronchopneumonia and apical tuberculosis. The duodenal stump and gastrojejunal anastomosis were well healed. The common bile duct and the duct of Wirsung had a common entrance into the duodenum.

In this case there was no gross evidence of obstruction to the pancreatic ducts. There was considerable evidence of local trauma combined with interference of the blood supply to the pancreas.

CASE 6. T. P. (N.E.D.H. 35106), a 52-year-old man, entered the hospital because of abdominal pain. The history, physical findings and laboratory data were consistent with acute appendicitis, and at operation a gangrenous, but nonperforated, appendix was removed. After operation, the patient was given penicillin and streptomycin. The postoperative course was characterized by persistent malaise, anorexia and vague abdominal pain. The temperature returned to normal on the 3rd postoperative day, and the wound healed without incident. He was discharged from the hospital on the 7th day.

On the day of discharge from the hospital he experienced slowly progressive, poorly localized periumbilical pain, which bored through to the back. There was continued anorexia and nausea, but no vomiting. The pain persisted, and 3 days later he was readmitted to the hospital.

On readmission the temperature was normal, and the pulse 110. The patient was pale and appeared moderately ill. Abdominal examination disclosed diffuse tenderness, especially in the upper abdomen and periumbilical area. There was no spasm, and peristalsis was normal. Rectal examination was negative. A plain x-ray film of the abdomen showed dilated loops of small bowel consistent with a paralytic ileus. An electrocardiogram demonstrated normal tracings. Examination of the blood revealed a white-cell count of 10,600 and a hemoglobin of 14.7 gm. per 100 cc. The serum amylase was at the upper limits of normal, and on the 3rd day after operation it was 330 units per 100 cc. — considerably above the normal range. The patient was treated conservatively, again being given antibiotics and continuous intestinal suction. The blood amylase had returned to normal by the 7th hospital day.

The diagnosis of pancreatitis in this case was a clinical one, resting on the unusual signs and symptoms and the associated elevation of the serum amylase. The etiology of the pancreatic inflammation and its relation to the operation were obscure. Pancreatitis has been described previously after operations on the thyroid and prostate glands and after fractures and neurosurgical operations. One must assume either that the relation is purely coincidental or that there may be factors initiated by an operation that contribute to the development of pancreatitis.

CASE 7. M. O. (P.B.B.H. 9B588), a 31-year-old woman, was admitted to another hospital because of vaginal bleeding in the 7th month of pregnancy. Physical examination showed no abnormalities. Laboratory data disclosed a moderate anemia for which the patient was treated by transfusion. This was followed by the onset of headaches, substernal pain, a shaking chill and peripheral vascular collapse. Because of continued vaginal bleeding, cesarean section was performed, and transfusions were continued — a total of 1500 cc. of blood having been given. The patient became oliguric and remained hypotensive. She was transferred to this hospital on the 3rd day after operation.

Physical examination disclosed a temperature of 99.8°F., a pulse of 152 and respirations of 26 per minute; the blood pressure was 100/80. The patient was pale and sweating. The abdomen was profusely tender, but peristalsis was normal. There was no distention. Examination of the blood showed a hematocrit of 36 and a white-cell count of 25,000. The urine contained a large amount of protein and gave a test for sugar; the sediment contained 20 to 40 white blood cells per high-power field. The blood urea nitrogen was 33 mg. per 100 cc. The carbon dioxide and chloride were normal; the serum sodium was 143 milliequiv., and the potassium 5.0 milliequiv. per liter.

The hospital course was a progressive one characterized by a maximum temperature of 105°F. daily. The abdominal signs persisted, and a mass in the right side of the pelvis, believed to be a hematoma in the broad ligament, gradually developed. The urinary output remained low, and there was continued azotemia. The patient died on the 6th hospital day, having been totally anuric and without an obtainable blood pressure for 48 hours before death, which was characterized by coma and convulsions.

At post-mortem examination there was a large infarct in the pancreas, with associated hemorrhage and fat necrosis.

There was a massive retroperitoneal hematoma and marked degenerative changes in the renal tubules. There was an extensive central lobular necrosis of the liver.

The remarkable feature of the examination, however, was the extensive pancreatic necrosis, which was associated with major thromboses of vessels in the head of the pancreas. Obstruction of the main pancreatic duct had occurred in the area of infarction. There was diffuse dilatation of pancreatic acini associated with inspissated secretion proximal to the area of infarction.

This was an extraordinary case, and the relation between the pancreatitis and the cesarean section or the transfusion reaction is by no means clear. This case is presented, however, because it represents acute, massive, apparently primary thrombosis of the major vessels to the head of the pancreas. The infarction and the inflammatory reaction subsequent to this thrombosis appeared at autopsy to have been directly associated with obstruction to the pancreatic ducts and dilatation of acini and accumulation of inspissated material proximal to the site of the thrombosis. The sequence of events, therefore, was not greatly different from that following primary vascular disease with occlusion of vessels leading to the pancreas.

Case 8. R. L. (P.B.B.H. U421) a 49-year-old widow with 1 child was admitted to the hospital because of "indigestion," epigastric pain, and belching after meals. A gastrointestinal series before admission had revealed a filling defect in the region of the ampulla of Vater. The symptoms had been present for approximately 18 months, and were frequently relieved by "soda."

The patient had had a cholecystectomy 18 years before. Diabetes had been discovered in 1951. The past history was otherwise noncontributory.

Physical examination disclosed an obese patient in no distress. There was no icterus. The heart and lungs were normal. The abdomen was normal except for well healed cholecystectomy and appendectomy scars. The liver, spleen and kidneys were not enlarged. Rectal and pelvic examinations were negative. The extremities were not remarkable.

The temperature was 98.6°F., and the pulse 82 per minute; the blood pressure was 144/76.

The hematocrit, white-cell count, total protein, blood urea nitrogen, bilirubin, serum chloride and carbon dioxide combining power were normal. The blood sugar was 112 mg. per 100 cc. Examination of the urine showed no abnormality.

A duodenal drainage was carried out the day after admission and proved to be negative for malignant cells, cholesterol crystals and other abnormalities. Because of the persistent filling defect within the 2d portion of the duodenum, operation was undertaken. An annular, uninflamed, aberrant pancreas was found encircling the 2d portion of the duodenum and apparently unconnected to the main pancreas, which was normal to palpation. There was no evidence of acute or chronic inflammation. The surgeon excised the aberrant portion of the pancreas from the duodenal wall without opening the duodenum and without disturbing the main portion of the pancreatic head or body. A frozen-section report was that of normal pancreas. The permanent report of this tissue removed was that of chronic pancreatitis with fibrosis.

Postoperatively the patient ran a temperature of 101°F. for 5 days. At the end of the 1st week, there was evidence of pyloric obstruction, but she had no abdominal pain and no fever. On the 10th day the serum amylase was reported as 515 units per 100 cc. Abdominal palpation revealed a tender mass in the epigastrium. A barium-swallow examination demonstrated thickened gastric rugae and an extrinsic pressure defect involving the greater curvature of the antrum and apparently arising posteriorly from the region of the pancreas. There was evidence of incomplete pyloric obstruction secondary to this extrinsic pressure. The mass persisted in spite of a rapid fall of serum amylase to 51 units per 100 cc. by the 13th postoperative day. Because of continued duodenal and pyloric obstruction, secondary to pancreatitis, a posterior gastroenterostomy was carried out on the 22d postoperative day. A fist-sized mass of fibro-fatty tissue involving the head of the pancreas was found. Postoperatively, the patient continued to have a degree of gastric retention for 2 weeks and became acutely alkalotic on one occasion during this time. However, by the end of the 3d week after the 2d operation, she was able to take nourishment well by mouth. She was discharged 23 days after the 2d operation. An x-ray film taken 1 month after discharge continued to show slow emptying of the stomach through both the gastroenterostomy and the pylorus. There was a moderate gastric residue. There was persistent narrowing of the 2d portion of the duodenum. The patient clinically was doing quite well, with no evidence of recurrent pancreatitis.

This case of postoperative pancreatitis re-emphasizes the complications resulting from trauma to any part of the pancreas. The development of pancreatitis after excision of an annular pancreas is unusual. It suggests that in this case the aberrant nodule had ducts that communicated with the main gland. The episode points again to the importance of local trauma and potential ductal obstruction in the etiology of this disease.

Discussion

Against the background of what seems to be a rational explanation of the pathogenesis of acute pancreatitis, it is difficult to understand why the condition developed in some of these cases. Obstruction of the main pancreatic duct can be excluded in Cases 1, 3, 5 and 7; it is extremely unlikely in Cases 6 and 8. Ductal obstruction was probably a primary factor in Case 2 and a significant secondary factor in Case 7, in which an area of infarction of the pancreas resulted in obstruction of the main duct. Occlusion of the duct of Santorini may have occurred in Case 3, but, unfortunately, no attempt to demonstrate it was made during the post-mortem examination. An obstruction of accessory ducts may have occurred in Case 8.

One cannot help being struck by the prominence of the vascular factor in some of the cases. In Case 3 a sizable pancreatic vessel was ligated (Fig. 1). In Case 5 occlusion of a major branch of the pancreaticoduodenal artery was found at autopsy, and in Case 7 a primary thrombosis of all the major vessels of the head of the pancreas was present. The location of these occlusions outside the gland suggests that they are not related to extravasation of pancreatic secretions. Although it is generally accepted that the pancreas is so richly supplied with blood that significant ischemia will not result from division of individual vessels around its head it may well be that if this is combined with comparatively mild degrees of local trauma, partial obstruction of the pancreatic ducts or sludging of the pancreatic secretions, a situation analogous to Popper's experimental studies, is established. In this respect particular attention is called to the vulnerability of the posterior pancreaticoduodenal artery (retroduodenal artery),[14] as shown in Figure 1. It is well known that ligation of this artery alone has

no ill effects, but when combined with trauma or ligation of the duct of Santorini or sludging of the pancreatic secretions, ligation may be of great significance.

The onset of mild pancreatitis after appendicitis (Case 6) is interesting and, together with the inadequate etiologic factors demonstrable in Cases 1 and 3, has made us wonder whether nonspecific factors associated with a surgical operation may contribute to the development of pancreatitis. In a series of 50 cases in which major trauma to the pancreas could be excluded, we have followed the levels of the serum amylase before and after operation.

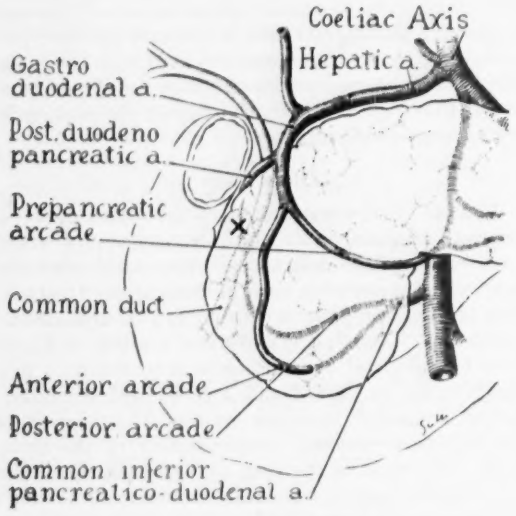

FIGURE 1. *The Course of the Posterior Duodenopancreatic Artery ("Retroduodenal Artery").*
Division of this vessel readily occurs during mobilization of the duodenum. X indicates the point of ligation in Case 3.

No significant elevations were found, but in 3 cases in which the pancreas was palpated or the operation was in the immediate vicinity of the pancreas, transient elevations occurred. In no case did the serum amylase rise to abnormal levels, however.

Rich[5] found histologic evidence of what he interpreted as a thickening and sludging of pancreatic secretions in some cases of acute pancreatitis in which an occlusion of a major duct could not be demonstrated. He postulated that changes in the character of the pancreatic secretions might lead to functional obstruction of small ducts, especially if associated with metaplasia of ductal epithelium. The volume of pancreatic secretions has been shown to be reduced by dehydration, atropine and ether anesthesia, all of which are factors frequently present in surgical operations.[18] Following these leads, we have made some preliminary observations on changes in the viscosity of pancreatic secretions before and after surgical operations.

Secretions were obtained by duodenal aspirations before and after operation, and the viscosity determined by the Ostwald viscosimeter. The studies of Shwachman and Patterson[16,17] indicate that the increased viscosity of duodenal contents is largely due to altered pancreatic secretions. They have found the viscosity of duodenal contents to be elevated in children with pancreatic fibrosis. Patterson noted an increased viscosity of duodenal secretions in a small number of adults with varying degrees of chronic pancreatic inflammation.

Of the 8 cases in which we carried out duodenal intubation before and after operation significant elevation of the viscosity of the secretions was found in 4. The procedures consisted of 1 colectomy, 6 operations on the biliary tract and 1 laparotomy in which an inoperable tumor of the pancreas was palpated. The highest elevation of viscosity occurred in cases in which the pancreas was manipulated or palpated, but in none was the organ traumatized or mobilized.

Although these observations are preliminary in scope and cannot be regarded as conclusive, they suggest that alterations in the volume and viscosity of pancreatic secretions may be a contributing factor in the development of postoperative pancreatitis in that such changes favor obstruction in the smaller ducts.

Summary and Conclusions

Acute postoperative pancreatitis is a tragic and somewhat inexplicable accompaniment of surgical operations. It occurs more frequently than has been supposed, and may follow operations in which trauma to the pancreas, reflux of bile into the pancreatic ducts or obstruction of the main pancreatic ducts can be excluded. Usually, however, it follows operations on the biliary tract and stomach in which mobilization and manipulation of the pancreas occur.

Minor interference with the blood supply to the pancreas may be an important factor if combined with trauma to the gland or partial obstruction to the pancreatic ducts. The posterior pancreaticoduodenal artery and the duct of Santorini are particularly vulnerable to injury when the duodenum is mobilized during gastrectomy.

In cases in which major obstruction or injury to the ducts can be excluded, sludging of the pancreatic secretions incidental to medication, dehydration or other factors associated with surgical operations may be a contributing factor that merits further investigation.

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EPIDEMIC HEPATITIS

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AN epidemic of hepatitis occurred in Uttar Pradesh, India, during the months of May to September, 1949. Some of the 88 patients studied had been admitted to S. N. Hospital and the Military Hospital in Agra and to the P. L. Sharma Hospital, Police Hospital and Dufferin Hospital in Meerut.

TABLE 1. *Clinical Diagnoses in 88 Cases of Epidemic Hepatitis.*

DIAGNOSIS	NO. OF CASES
Pregnancy with jaundice	11
Acute yellow atrophy of liver	2
Pregnancy with toxic jaundice	3
Acute infectious hepatitis	39
Endemic ascites	5
Portal cirrhosis	4
Cancer of liver	2
Precirrhotic hepatitis	1
Hepatitis	1
Jaundice	16
Acholuric jaundice	1
Cholemia	1
Acute poisoning	1
Heart failure	1

There were various clinical diagnoses (Table 1). Twenty patients died. Liver biopsy was performed in most cases.

Three adult patients, as well as 4 fetuses of women with fulminant epidemic hepatitis who later died, were completely studied at autopsy. In these 88 cases, 20 of which were fatal, 37 patients were females and 51 males (Table 2).

Eighty per cent of all fatal cases were in women, 81 per cent of whom were pregnant (Table 3). Epidemic hepatitis attacking young pregnant women proved fatal in most cases.

For convenience of description we have separated the disease into three phases: preicteric, icteric and posticteric or convalescent.

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PREICTERIC STAGE

The preicteric phase in the great majority of patients lasted nine days or less but varied from one day to as long as several weeks (Table 4). In some cases it was difficult to discover exactly when the jaundice first appeared because the patients came from villages and did not realize that they had jaundice until they were deeply yellow. The cases in which more than fifty days elapsed between onset of symptoms and jaundice probably fall in this group.

TABLE 2. *Age, Sex and Race of 88 Patients with Epidemic Hepatitis.*

AGE	MALES	FEMALES	HINDUS	MUSLIMS	CHRISTIANS	TOTAL
yr.						
10–14	1	0	1	0	0	1
15–19	5	3	5	2	1	18
20–24	10	17	26	1	0	27
25–29	7	4	10	1	0	11
30–34	6	6	11	1	0	12
35–39	9	3	11	1	0	12
40–44	5	2	6	0	1	7
45–49	3	1	3	1	0	4
50–54	4	0	4	0	0	4
55–59	0	1	1	0	0	1
60–64	1	0	1	0	0	1
Totals	51 (60%)	37 (42%)	79 (90%)	7 (8%)	2 (2%)	88

TABLE 3. *Age and Sex in 20 Fatal Cases of Epidemic Hepatitis.*

AGE	FEMALES		MALES
	PREGNANT	NONPREGNANT	
yr.			
15–19	2	0	0
20–24	8	1	0
25–29	1	0	0
30–34	2	0	2
35–39	0	1	2
40–44	0	1	0
Totals	13 (65%)	3 (15%)	4 (20%)

The initial symptoms were somewhat different in fatal and nonfatal cases (Tables 5 and 6). Two patients had no preicteric symptoms and dated their illness from the appearance of jaundice. The initial symptoms may have been so mild that they passed unnoticed. However, in 30 per cent of fatal cases jaundice was the initial symptom. All these patients were pregnant women, most of whom were under constant observation in the antenatal clinics.

TABLE 4. *Interval between Onset of Symptoms and Appearance of Jaundice in 75 Cases of Epidemic Hepatitis.*

DAYS	NO. OF CASES
1–4	58
5–9	5
10–14	0
15–19	0
20–24	2
25–29	4
30–34	1
35–39	0
40–44	0
45–49	0
More than 50	5

TABLE 5. *Initial Symptoms in 64 Nonfatal Cases of Epidemic Hepatitis.*

SYMPTOMS	NO. OF CASES	PERCENTAGE
Fever	28	43.7
Anorexia	12	18.4
Pain in right hypochondrium	6	9.3
Nausea	4	6.2
Body pains	2	3.1
Headache	2	3.1
High-colored urine	2	3.1
Chill	1	1.5
Dyspepsia	1	1.5
Diarrhea	1	1.5
Constipation	1	1.5
Abdominal heaviness	1	1.5
Colicky pains	1	1.5
No preicteric symptoms	2	3.1

After the preicteric stage of epidemic hepatitis the patients either continued a mild course with no development of jaundice (8 per cent of the nonfatal cases) or rapidly became moderately or deeply jaundiced (92 per cent of the nonfatal cases).

TABLE 6. *Initial Symptoms in 20 Fatal Cases of Epidemic Hepatitis.*

SYMPTOMS	NO. OF CASES	PERCENTAGE OF CASES
Fever	7	35
Jaundice	6	30
Deep coma	2	10
Pain in right hypochondrium	1	5
Headache	1	5
Unconsciousness	1	5
Vomiting	1	5
Hemorrhagic phenomena	1	5

Epidemic Hepatitis without Jaundice

Three of the 5 patients were males, and 2 were females. One of them was twenty-three years old, and the remainder were between thirty and fifty years of age. Only 1 case was diagnosed initially as hepatitis. The duration of illness on admission was three and a quarter to three and a half months in 2 cases, four months in the other 2 and nine months in the remaining case. The symptoms were milder in these cases than in those of the icteric type. One patient had a rise of temperature; the others were afebrile. The disease started with vague gastrointestinal symptoms, such as constipation, diarrhea, eructation, abdominal discomfort and actual pain. Anorexia was an early symptom in 2 of these cases, whereas in the remaining 3 it followed the other symptoms. Vomiting did not occur. Early fatigability was a common complaint. The liver was enlarged, firm and tender in only 2 cases. Fluid was present in the abdominal cavity to a greater or lesser extent in 4 cases. The serum bilirubin was normal in 2 cases and only slightly raised in the other 3.

ICTERIC STAGE

The transition from the preicteric to the icteric stage was marked by the appearance of dark urine and jaundice. Jaundice usually followed fever but occasionally developed simultaneously with fever. In 30 per cent of the fatal and 6 per cent of the nonfatal cases it was the initial symptom. The duration of icterus was variable, ranging from about fifteen days to six months or more. Ten per cent of the cases were in the last category.

The icteric stage became fulminant (fatal), or the patient recovered normally, had a delayed recovery with recrudescence or had chronic hepatitis, including postnecrotic fibrosis and nodular hyperplasia.

Fulminant, fatal type. Sixteen of the 20 fatal cases studied in this series belonged to this type. Thirteen patients in the entire series were pregnant and below thirty-four years of age. Nine were five or six months pregnant. There was no particular relation of hepatitis to parity in these cases. In 12 cases the symptoms lasted from one to thirteen days. In the remaining case the duration was one month. In 8 of these 13 cases the disease pursued a fulminant course from the start. In 4 cases it took two to ten days for the disease to turn suddenly grave. In the remaining case the disease took a serious turn on the twenty-eighth day.

It is interesting that the majority of fulminant, fatal cases occurred in pregnant women—a fact that has not been mentioned by previous writers, most of whose studies have been on military personnel.

In these patients high fever, deepening jaundice, toxemia and various nervous manifestations were present from the start or developed within a few days of the onset. The increasing toxemia was manifested in one or more of the following ways: restlessness, headache, severe aching in the body, breathlessness, deepening jaundice, high fever,

continuous vomiting, epigastric pain, increasing anorexia, hemorrhages, rigors, twitchings, delirium and semicoma progressing to coma.

In the terminal phases of the illness the respiration was usually labored, hemorrhages were common, and nervous manifestations were generally present.

In 16 of the 20 fatal cases studied, nervous manifestations either were present from the start or developed in the later stages. Death occurred in 88 per cent of cases within four days and in the rest within nine days of the onset of symptoms of cerebral involvement.

Post-mortem examinations were performed on 4 fetuses delivered of the mothers who died of fulminant hepatitis. Three showed no specific findings, and 1 had changes characteristic of epidemic hepatitis.

Normal recovery. Fifty-two out of 68 nonfatal cases belonged to this group, comprising 76 per cent of the nonfatal cases. Of these 52 patients 13 were pregnant. In the remaining 39 cases 4 were females, and 35 were males. The ages varied from thirteen to fifty years.

After the jaundice had initially subsided to a low level convalescence began. Rest in bed and continued convalescent treatment of the patient for periods ranging from two to four weeks after disappearance of jaundice (Table 7) were essential for a normal recovery.

In contrast to the fulminant cases, in which deepening jaundice, toxemia, hyperpyrexia and nervous manifestations developed, these patients were completely afebrile soon after the decrease of jaundice and had no nervous manifestations. Symptoms of toxemia rarely if ever developed.

Delayed recovery. In 8 of the 88 patients convalescence was interrupted by recrudescences or relapses, which occurred mostly in the posticteric stage. These patients usually had nausea and malaise, dark urine and increase of serum bilirubin; the liver was usually enlarged and tender.

There was a definite relation between the degree and early resumption of exertion to the severity of relapse. Duration of relapse was usually short, and the patients recovered satisfactorily.

In this group one patient continued to have complaints of anorexia, fatigue and abdominal discomfort for a long time after apparent recovery from epidemic hepatitis, in spite of normal histologic and biochemical findings. This condition has been termed "posthepatic syndrome."

As in other reports the commonest factor responsible for relapse was cutting short of convalescence and early resumption of hard work.

Chronic hepatitis. The progression of a small percentage of cases of acute hepatitis to a chronic form developing finally into nodular hyperplasia, postnecrotic fibrosis, diffuse portal cirrhosis or so-called cholangiolitic cirrhosis has been suggested by various workers. During the course of the present investigation we came across cases that on histologic examination of the liver-biopsy specimen could be grouped as postnecrotic fibrosis and nodular hyperplasia. Most of these cases were reported in a previous study.[1]

Laboratory and Pathological Data

The white-cell counts in the 88 cases ranged from 4000 to 38,000. If the fatal and nonfatal cases are considered together 63 per cent had either leukopenia or normal counts; 22 per cent had counts between 10,000 and 12,000. It is of interest that in 75 per cent of the fatal cases the white-cell counts were about 10,000, whereas 70 per cent of the patients in the nonfatal cases had leukopenia or normal counts during the febrile or preicteric stage and shortly thereafter.

The differential white-cell count showed relative lymphocytosis throughout the disease in 64 per cent of the nonfatal and 20 per cent of the fatal cases. In the nonfatal cases without lymphocytosis the counts were done in the late stages of the disease, because of the late admission to the hospital. Eighty per cent of the fatal cases showed relative or absolute leukocytosis.

Table 7. *Interval before Disappearance of Icterus in 52 Nonfatal Cases with Eventual Normal Recovery.*

Interval Before Clearance of Icterus	Percentage
wk.	
1–4	61.5
5–7	17.3
8–10	3.8
11–13	13.5
14	3.8

The pathological findings in the fatal cases of epidemic hepatitis can be placed in two main classes: fulminant and subacute. The chief microscopical findings are extensive autolytic necrosis of the liver cells and interlobular and periportal cellular infiltration by lymphocytes, histiocytes and plasma cells. Varying numbers of polymorphonuclear leukocytes and eosinophils are also present. Polymorphonuclear leukocytes are also present in the liver cells undergoing necrosis. The necrosis is invariably central and involves the parenchyma completely and uniformly so that in most cases only a rim of liver cells is seen at the periphery of the lobule. Reticulum staining reveals the reticular framework to be intact. The central veins in most of the cases show fibrinoid necrosis of their walls and endophlebitis. The sinusoids appear widely engorged and contain erythrocytes and inflammatory cells. There is no evidence of regenerative hyperplasia of the surviving parenchyma. In some cases proliferation of the biliary epithelium is present even at this early stage. Bile thrombi can be seen inside these proliferated bile ducts. Within the lobular remnants, macro-

phages containing lipochrome can be seen. This last finding was, however, more commonly seen in the subacute cases.

In the subacute form necrosis of the hepatic parenchyma is patchy and irregular. Regeneration of the liver cells varies from the presence of large and multinucleate cells at the periphery of the lobule to nodular regeneration. The regenerative nodules are completely devoid of normal lobular architecture. Inflammatory cells, chiefly mononuclear leukocytes, are seen in the portal areas and interlobular tissues. In foci of necrosis condensation of reticulum is present. In some cases adult fibrous tissue is observed.

In spite of the frequently severe symptoms referable to the central nervous system in fulminant, fatal cases, the histologic changes in the brain consist only of swelling of the ganglion cells, with distortion of their nuclei. In subacute, fatal cases there is lymphocytic infiltration in the meninges and a perivascular lymphocytic infiltration in the basal ganglions. In one case ganglion cells in the lenticular nucleus were swollen and showed cytolysis and deposition of dark-yellow pigment inside them. This condition — "kernicterus" — is rare in adults although it has been reported by Rutledge and Neubuerger.[2]

Serial liver biopsies were performed in a number of cases to study the progression of epidemic hepatitis. The following case showed progression of acute to chronic hepatitis:

H. S., a 25-year-old Hindu man, was admitted to the hospital with the clinical diagnosis of hepatitis.

The first biopsy was performed on August 31, 1949, showing the pattern of the liver lobule to be normal. The liver cells demonstrated a patchy autolytic necrosis and cytoplasmic depletion. Scattered multinucleate cells were present. The sinusoids were distended and contained mononuclear cells. There was periportal and perilobular infiltration with mononuclear cells.

Liver biopsy, performed on September 18, revealed derangement of the normal cellular pattern of the hepatic lobule and marked infiltration of the perilobular connective tissue with mononuclear cells and lymphocytes. Central necrosis was prominent, the liver cells showing eosinophilic hyaline and hydropic degeneration. The sinusoids were distended and filled with mononuclear leukocytes; the reticuloendothelial cells were swollen. The central veins disclosed endophlebitis.

Biopsy on October 16 showed the hepatic cellular pattern to be still abnormal. The liver cells were swollen, and the cytoplasm was pale and granular. Evidence of regeneration was marked. Condensation of reticulum was seen. The sinusoids remained distended and still contained a moderate number of mononuclear cells. Inflammatory infiltration was observed throughout the parenchyma. There was increased fibrous tissue in the regions of necrosis. The central veins were thickened and narrowed. The bile ducts gave evidence of proliferation; no bile thrombi were seen.

Biopsy on November 14 revealed a disturbed hepatic structure, with definite postnecrotic fibrosis. Regeneration was evidenced by multinucleated cells. Pigmented nodules were seen though still in early stages. Study of these serial biopsies indicated ultimate development of chronic hepatitis and postnecrotic fibrosis in a patient with acute epidemic hepatitis who did not recover.

Discussion

The present study involved civilians. The mortality was 7.8 per cent among males and 43.2 per cent among females. The figure of 7.8 per cent mortality among Indian males is far too high as compared to the highest figure of 0.44 per cent in Western epidemics. The high mortality in Indians was confirmed by Witts,[3] who mentioned the difference in incidence of, and the mortality from, infectious hepatitis in the India Command during 1944. The incidence of jaundice was five times as high in the British troops as in the Indian troops, but the mortality was exactly the reverse. The factor favoring the low incidence of jaundice could be a nutritional difference or a previous exposure, but it is almost certain that the high mortality of Indians with the disease was due to malnutrition.

An important finding has been the high incidence of mortality among females (43.2 per cent in the present series), of whom 81 per cent were pregnant. It may be, therefore, that high mortality among the female patients was due not to difference in sex but to complicating pregnancy. Jersild[4] reported a serious epidemic of infectious hepatitis in Denmark associated with a high mortality among women after the menopause. In this epidemic 75 patients died, only 1 of them being a man; thus, 95 per cent of fatal cases occurred in women.[4] Several other observers[5-7] have had similar experiences. During an epidemic in Sweden in 1928 Bergstrand[8] found that 72 per cent of malignant cases of hepatitis occurred in women.

The majority of women in the Scandinavian epidemics were elderly. In the present series, the affected women were young (below thirty-four years of age). A feature common to most women in the Danish epidemic and the present cases is that they had either passed the menopause or had suppressed menses because of pregnancy. In the Danish epidemic, in several of the younger patients with chronic hepatitis the menses failed while the infection lasted, sometimes for more than a year. In the present series 2 women, who were not pregnant and who died, gave a history of amenorrhea. These facts make one wonder whether in some way the female sex hormone has a bearing on the course of the disease. Similar suggestions have been made by Jersild.[4]

From our experience we believe that epidemic hepatitis when it becomes chronic ends in postnecrotic scarring and not in diffuse hepatic fibrosis, cholangiolitic cirrhosis or hypertrophic biliary cirrhosis.

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RUPTURED MYOCARDIAL INFARCT WITH SURVIVAL FOR THREE WEEKS

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IT is apparent from a review of the literature that rupture of the heart is an important consideration in the complications of acute myocardial infarction. Usually, death occurs forthwith. In the case reported below, there was an opportunity during the clinical course to make a diagnosis of hemopericardium from cardiac rupture. So rare is such a condition that when the x-ray silhouette of the heart with an established infarction shows what appears to be a "pericardial effusion" and fails to clear, there is justification for doing a pericardial tap to make a precise diagnosis.

CASE REPORT

C. A., a 64-year-old tailor, shortly after midnight on September 4, 1950, was awakened by persistent, agonizing "vise-like" lower substernal pain that extended upward to the left shoulder and was associated with profuse sweating and marked breathlessness. The patient attributed the attack to "acute indigestion" brought on by a supper of 2 soft-boiled eggs. His physician, called in during the early morning hours, administered 2.5 mg. of morphine and 0.4 mg. of atropine intravenously and forthwith sent the patient by ambulance to the hospital, where he was immediately placed in an oxygen tent and treatment was instituted for acute coronary occlusion.

The patient had always been in good health, despite extremely sedentary habits but he was a nervous and apprehensive person. After a careful checkup 1 year before the present illness, a diagnosis of "anxiety neurosis" was made. No evidence of cardiac or other illness was found. There was reference to a spell of transient precordial chest pain in 1946, but the patient had no apparent sequel and denied any recurrence of chest or epigastric pain until the onset of the present illness.

Physical examination disclosed an acutely ill man who was extremely apprehensive. He appeared somewhat pale and demonstrated moderate cyanosis of the lips and the nail beds. The skin was clammy. He complained of pain localized in the midepigastrium, and in the left side of the chest, which was moderately emphysematous, with poor excursions. The lungs were clear. The heart sounds were of poor quality and distant, and no murmurs or friction rub was heard.

The blood pressure was 120/84. The pulse was 120, and the heart rhythm was regular.

The urine was normal. Examination of the blood showed a red-cell count of 4,850,000, with a hemoglobin of 14 gm. per 100 cc., and a white-cell count of 15,000, with 82 per cent neutrophils and 18 per cent lymphocytes. The sedimentation rate was 3 mm. in 1 hour (Wintrobe method). An electrocardiogram on September 6 demonstrated a regular rate of 140, low QRS complexes, elevated ST segments and diphasic T waves in Leads 1 and 2, with absent R waves in the CF series and elevated ST segments in Leads CF_2 to CF_5, with inverted T waves. The pattern was interpreted as diagnostic of acute anterior myocardial infarction.

The patient was critically ill for the remaining 27 days of his life, requiring oxygen and repeated 100-mg. doses of Demerol or 2.5-mg. doses of morphine or the equivalent, as well as other sedatives, aminophylline and mercurial diuretics. He constantly suffered from chest pain, except as relieved by narcotics, and from breathlessness, in spite of generous use of oxygen by the tent method. Another troublesome feature was extreme apprehension and episodes of mental excitement and confusion. At no time was a friction rub or heart murmur identified, and the heart sounds remained of poor quality.

On the 2d hospital day, after a small saline enema, the patient began to groan and strain, and then suddenly collapsed, becoming pulseless, semicomatose, dyspneic, cyanotic, pale and sweaty. The blood pressure was unobtainable. He vomited about 400 cc. of brownish, liquid food.

During the rest of the week, chest pain, dizziness and restlessness persisted. The pulse, not always obtainable, was regular and of poor quality. The blood pressure was at times unobtainable, with "tappings" at 90 to 110. The temperature tended to run about 100°F. and on one occasion was 102.6°F. The pulse varied from 100 to 140; there was some abdominal distention, but no tenderness.

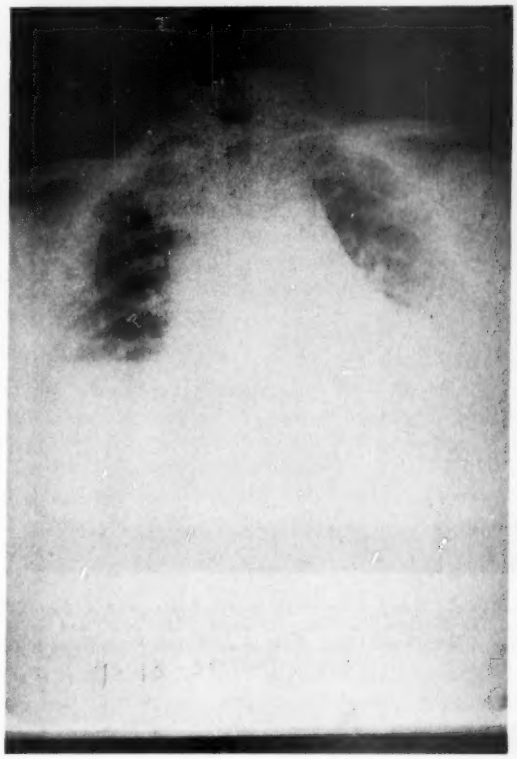

FIGURE 1. *X-ray Film of the Chest Taken with a Portable Machine Eight Days after the Onset of the Illness and Six Days after the Second Episode of Acute Circulatory Collapse.*

During the 2d week, an x-ray film of the chest showed both leaves of the diaphragm to be high, with clear lungs in the upper half of the chest. The hilar shadows were markedly widened from the cardiac borders to the neck. The smooth contour of the enlargement was considered consistent with "pericardial effusion" (Fig. 1). The patient remained dyspneic. The blood pressure was 110/90. The area of cardiac dullness extended 3 cm. to the left of the nipple line. The

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heart sounds were barely audible. The white-cell count was 30,050, and the sedimentation rate 33 mm. in 1 hour (Wintrobe method). At this time a 2d cardiac consultant reviewed the findings to date. A repeat electrocardiogram showed further minor changes considered consistent with the progress of a massive myocardial infarction complicated by pericarditis, effusion and a failing myocardium. A pericardial tap was considered but postponed because, if the apparent pericardial effusion was a transudate and a complication of the infarction, as seemed likely, it would spontaneously disappear with improvement; if it was a hemopericardium, the

FIGURE 2. *X-ray Film of the Chest Taken with a Portable Machine Eighteen Days after the Onset of the Illness and Eight Days before Death (This Film Was Taken Four Days after the Diagnostic Pericardial Tap).*

situation was presumably hopeless. An infectious pericarditis seemed unlikely.

As the 2d week of acute illness drew to a close the patient's course continued critical, as evidenced by breathlessness, chest pain and mental symptoms. The blood pressure was 110/90; the neck veins were prominent, and the pulse rate was 110. The area of cardiac dullness extended to the left axillary line. The heart sounds were inaudible. Repeat x-ray films of the chest taken with a portable machine on the 14th hospital day suggested increasing pericarditis with effusion and cardiac edema, hemopericardium not being excluded. Repeat electrocardiograms showed minor changes compatible with the course of anterior myocardial infarction with pericarditis.

During the 3d week of illness a pericardial tap was done to establish the nature of the pericardial effusion and to provide relief if possible. After suitable preparation of the operative site on the chest, a 20-gauge spinal needle was introduced about 2 cm. inside the area of dullness at the 5th interspace 1 cm. lateral to the nipple; 100 to 120 cc. of bright-red blood was removed with difficulty, owing to clots. Hemopericardium had evidently complicated myocardial infarction and was most probably due to ruptured heart. (The culture of this fluid was later reported as negative for bacterial growth.) During the rest of this week the patient's condition remained about the same or was possibly a little improved. He was allowed out of the oxygen tent intermittently. A repeat x-ray film, however, revealed the same cardiac silhouette (Fig. 2).

Late on the 25th day of illness the patient suffered an acute episode of precordial pain. He became pale and sweaty and felt as though he were "going to die." The pulse although regular at 140 had a poor quality, and the blood pressure was 85/70. In the course of 3 hours, a total of 200 mg. of Demerol and 2.5 mg. of morphine were given to relieve increased pain in the chest.

His condition became progressively worse, and on the 26th day the heart sounds were no longer audible and the blood pressure had fallen to 80/70. On the following morning he experienced a return of severe chest pain and died.

At autopsy the pericardial sac was much enlarged and contained approximately 800 cc. of clotted blood. The pericardium was thickened, with organized clot and adhesions throughout but most marked at the posterior diaphragmatic area. The anterior surface of the heart was covered with fibrin and blood clot, and the apex of the left ventricle was grayish white over an area 6.5 by 4 cm. At the proximal margin of this area just lateral to the posterior longitudinal sulcus there was a tear of the epicardium 1.5 cm. wide and extending distally and laterally about 2 cm., through which both organized red-cell clot and dense, fibrous, white scar tissue could be seen. A 2-mm. metal probe directed over this area fell by its own weight through into the left ventricular cavity.

The heart weighed 864 gm. The right atrium was dilated. The wall of the right ventricle measured 4 mm., and the left 20 mm. in thickness. The valves were normal. The endocardial surface of the left ventricle was smooth except at the apex, where an area 10 cm. wide and 6 cm. from the tip toward the base extending along the interventricular septum appeared reddish white. At the upper margin of this area at the posterior margin of the septum a loosely organized blood clot was noted, on removal of which a 2-mm., slit-like opening permitted the passage of a probe to the exterior. All branches of the coronary arteries showed sclerosis, and the left anterior descending artery was occluded by a red-and-gray-streaked thrombus starting 2 cm. from its origin over a distance of 3 cm.

Cross-section through the left ventricle from the area of epicardial discontinuity proximally along the posterior margin of the interventricular septum showed a myocardium 2 cm. thick abruptly disappearing into a dense, white, fibrous subendocardial layer 1.5 cm. thick, a central layer of dark-red, soft blood clot 5 mm. thick and a soft, necrotic-appearing, brownish-gray layer measuring 4 mm. that was thought to be mostly epicardial fat externally.

Cross-section through the apex of the left ventricle distal to the area of epicardial discontinuity on the diaphragmatic surface of the ventricle showed a 7-mm.-thick, fibrous, firm endocardial layer, a layer of dark-red clotted blood and soft gray-brown myocardial strands measuring 1.2 cm., a subepicardial layer of fresh dark-red soft clotted blood measuring 7 mm. and a 2-mm. epicardial layer of fibrin and organized blood clot.

The rest of the examination was limited to the lungs, which demonstrated nasal atelectasis.

On microscopical examination, sections through the epicardium from all areas revealed a thick layer of adipose tissue covered or partially infiltrated with granulation tissue. Adjacent to this granulation tissue was a lamina of organizing fibrin, and superficially forming the pericardial surface were strands and masses of fibrin intermixed with red blood cells. The muscle through the thinned apical area demonstrated replacement of myocardium by vascular, loose, fibrous connective tissue containing many macrophages, some of which contained yellow-brown pigment. A few fragments of muscle fibers remained in the area. Adjacent to the areas of fibrous myocardial replacement were broad expanses of necrotic muscle fibers devoid of nuclei and cellular detail. At the junction of the two types of tissue there were a few scattered neutrophilic leukocytes. The necrotic muscle fibers were more prominent in the area adjacent to the endocardium, and the fibrous replacement was more prominent next to the pericardium. Through the remainder of the heart there was

normal myocardium covered externally by organizing hemorrhage. Overlying the endocardial surface of the infarct and of the adjacent endocardium was an extensive mural thrombus composed of homogeneous, eosinophilic staining material. Section of the left anterior descending coronary artery, through the area of gross occlusion, showed an organizing red thrombus.

The final anatomic diagnoses were coronary sclerosis, with recent thrombosis of the left anterior descending branch; recent infarction of the apex of the left ventricle, with mural-thrombus formation; rupture of the left ventricle and organizing hemopericardium; and probable terminal hemorrhagic dissection from the rupture point between the old endocardial scar and the apical epicardium through the thin layer of subepicardial myocardium.

Summary

The clinical and pathological details of a case of moderately severe myocardial infarction complicated by cardiac rupture with hemopericardium of three weeks' duration are presented.

We are indebted to Dr. Paul D. White, of Boston, for his advice and encouragement, and to the Pathology Department, Dartmouth Medical School, especially Dr. John Holyoke, who kindly made the histologic studies.

MEDICAL PROGRESS

ENDOSCOPY*

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NO medical progress article on the subject of endoscopy has been published in this journal for about four years. Therefore it seems pertinent to review the literature and bring the subject up to date.

BRONCHOSCOPY

Physiology

Morton, Klassen and Curtis[1] have reported the literature pertaining to the lungs and tracheobronchial tree. Unilateral vagus section just below the recurrent laryngeal nerve but above the pulmonary plexus as performed in a series of patients with inoperable bronchiogenic carcinoma usually abolished pain of bronchial origin on the homolateral side. In 3 patients, after unilateral vagus section, electric stimulation of the homolateral main bronchus referred pain to the contralateral anterior cervical region. These data suggest that the afferent fibers that transmit pain from the bronchial tree are carried by the homolateral vagus nerve.

Technic

Emerson[2] has described an aspirating bronchoscope for the general surgeon, obstetrician and anesthetist. He has incorporated into one instrument the power supply, oxygen carrier and bronchoscope, thus eliminating battery boxes, transformers and light cords, lowering the cost and simplifying the whole bronchoscopic setup.

Weisel and Tella[3] have studied 1000 cases in which tetracaine (Pontocaine) was used as a topical anesthetic in bronchoscopy. There were 12 minor and 7 severe toxic reactions attributed to the anesthetic agent. The authors consider tetracaine hydrochloride an excellent agent for topical anesthesia, but believe that its danger must be appreciated. (I have given up the use of this agent because of the fatal cases reported in the literature.)

Holinger[4] has devised an upper-lobe bronchoscopic forceps that is flexible and can be guided into the various branches of either upper-lobe bronchus. The use of this biopsy forceps should result in more positive bronchoscopic biopsies in otherwise inaccessible bronchial tumors.

Bronchography

Peck, Neerken and Salzman[5] have presented a clinical and experimental study of the use of a new bronchographic medium. They believe that this material has several advantages over Lipiodol, chief among which are its water-soluble base and its rapid disappearance from the lung tissue, making x-ray studies in the period after bronchography more satisfactory.

Indications, Contraindications and Complications

Etsten and Mahler[6] report a series of 800 endotracheal intubations in 3 of which acute obstruction of the upper respiratory tract developed twenty-four to forty-eight hours after endotracheal anesthesia. The clinical picture was that of laryngeal edema: cough, hoarseness, stridor, dyspnea and suprasternal retraction. Without immediate therapy the complications of acute anoxia would have ensued. On direct laryngoscopic examination, the glottic chink, epiglottis and larynx appeared normal, and there was no evidence of laryngeal edema. Bronchoscopy, however, revealed an adherent subglottic membrane as the cause of the obstruction. The treatment of subglottic membrane is immediate bronchoscopy and removal of the débris. If the entire membrane is not removed it may recur in twenty-four hours. Tracheotomy is not necessary after complete removal of the membrane.

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Culver, Makel and Beecher[7] describe their experience after a dye was introduced into the stomachs of 300 unselected patients before operation. After surgery, the pharynx and bronchi were examined for staining. Regurgitation occurred in 26 per cent of these patients. Aspiration into the lungs occurred in 16 per cent. Silent aspiration was present in 8 per cent. Trendelenburg or lateral positions produced much more regurgitation than other positions. Patients of inexperienced anesthetists are more likely to aspirate. The authors conclude that an empty stomach during operation is absolutely essential. The importance of therapeutic postoperative bronchoscopic aspiration should be emphasized, and anesthesiologists should be trained to carry out this procedure.

Bronchial Obstruction

Shaw[8] reports at length on mucoid impaction of bronchi resulting from a localized accumulation of inspissated mucus in the bronchi in 10 patients between the ages of fourteen and fifty-seven, all of whom had an underlying condition of asthma or chronic obstructive bronchitis. Typically, it occurs in the second-order branch bronchi distal to a bifurcation. The impaction grows in size, layer by layer, in a laminated manner, finally dilating the bronchial wall. Operation may be indicated to rule out neoplasm or to remove segments of lung destroyed by suppuration beyond the impaction, or both.

Hodell[9] described 3 cases in which large cavities remained despite satisfactory artificial pneumothorax. Thoracotomy was not possible in 2 of these cases of far-advanced pulmonary tuberculosis because of serious involvement of the contralateral lung. Surgical aid was not available in the third. Uneventful recovery, with closure of the cavities and management of the coexisting endobronchial disease, was effected by bronchoscopic therapy in all 3 cases. The author discusses the importance of bronchoscopy as a means not only of identifying and removing obstructive bronchial plugs in such cases but also of identifying the source of a positive sputum and identifying and treating an active endobronchial lesion.

Rubin and Rubin[10] state that bronchial obstruction, with or without demonstrable atelectasis, may complicate a spontaneous or traumatic pneumothorax, preventing reaeration of the lung in spite of strenuous attempts to obliterate the pneumothorax space. It is essential, therefore, that in obstinate cases bronchoscopic aspiration be employed to cleanse the bronchi of secretion and allow ingress of air in addition to attempts at obliterating the pneumothorax space by conventional methods of treatment.

Holinger, Johnston and Basinger[11] describe benign stenosis of the trachea. The lesions consisted of congenital anomalies, specific and nonspecific inflammatory lesions and stenoses of traumatic origin. Case reports of each type are given and discussed. Of the total of 29 cases 12 were of congenital origin, and 17 were due to acquired lesions. In 5, the condition was attributed to trauma. The diagnosis was suspected from the history and physical findings, and confirmed by x-ray studies.

Gans and Potts[12] report the case of an anomalous lobe of lung arising from the esophagus. Bronchoscopic examination revealed a left-lower-lobe bronchus that was somewhat compressed posteriorly, with little air exchange in the left lower lobe. The left-upper-lobe bronchus was likewise compressed and had no air exchange whatsoever. A flexible, curved aspirator could be advanced only a few millimeters into this bronchus. During esophagoscopy a large amount of thick, yellow-green pus was aspirated. At about the level of the bifurcation of the trachea a fistula or diverticulum almost as large as the esophagus itself could be seen, and appeared to be lined with normal mucous membrane. With each respiration pus was expelled freely from this fistula into the lumen of the esophagus.

Gerson and Rothstein[13] describe a patient in whom a supernumerary tracheal bronchus to the right upper lobe was diagnosed by bronchoscopy and bronchography. The major right-upper-lobe bronchus occupied its normal position. The anomalous bronchus arose 5 cm. above the carina and was 2 cm. in length and 0.75 cm. in diameter. It supplied a small segment of the medial anterior portion of the right upper lobe.

Rosedale[14] points out that although bronchoscopy is relatively new in the newborn infant, it is an important salvage measure. It should be available in all hospitals with obstetric services. Pediatricians, who are oftenest called to see the newborn infant with atelectasis, should be familiar with the clinical pattern and the relatively easy method of treatment. Obstetricians are counseled to use the scientific direct visual method of bronchoscopy for restitution of the lower airway. All otolaryngologists are urged to familiarize themselves with this technical procedure. The co-operation of these three groups of specialists in this problem will lower the morbidity and the mortality rate among newborn infants. The procedure is practical, sensible, safe and life saving.

Reynolds and his associates[15] stress the value of tracheotomy in the postoperative care of patients subjected to esophagectomy. They believe pulmonary complications are likely to develop in such cases. These patients experience considerable difficulty in raising and expectorating mucus that accumulates in larger amounts than usual. Most of them are of an advanced age, with varying degrees of emphysema and pulmonary fibrosis, and some may have a mild degree of chronic bronchitis. At operation the tracheobronchial tree is aggravated by an endotracheal tube and by anesthetic gases.

Thorough tracheobronchopharyngeal toilet at the conclusion of the operation is obligatory. The use of tracheotomy to allow frequent aspiration or to provide an airway has become fairly well recognized, although the authors do not recommend tracheotomy in each esophagectomy but suggest its application in patients in whom audible rhonchi are heard soon after operation, indicating a voluminous quantity of mucus that cannot be expectorated.

Templeton[16] reports a case of bronchial obstruction with chronic atelectasis and pneumonitis due to hilar lymphadenitis after lobectomy and lingulectomy. The possibility of this unusual complication should be borne in mind during the performance of lobectomy when tissues to reinforce the bronchial stump are being selected so that the formation of a fixed lymphatic ring about the bronchus may be avoided.

Nonspecific Infectious Diseases

Callahan[17] describes a case of fibrinous bronchitis in which there was no evidence of tuberculosis. He states that fibrinous bronchitis has been recognized as a pathologic entity for many years, probably because of its outstanding characteristic, the expectoration of bronchial casts by the patient. The casts are expectorated as white masses in the sputum, which when floated in water can be made to unravel and show their branched form. No specific etiology is known. There are three cardinal symptoms: dyspnea, cough and expectoration of casts.

Tracheobronchial Tuberculosis

Froste[18] discusses bronchoscopy in pulmonary tuberculosis, presenting a clinical study of 1001 cases of bronchoscopic examinations. He considers bronchoscopy to be indicated in the following conditions: lymphadenitis with possible perforation; suspected specific process in the bronchial tree; suspected stenosis; valve mechanism; atelectasis; hemoptysis of doubtful origin; occlusion treatment; treatment by aspiration; secretion tests, whether to decide from which side the bacilli come or to obtain the secretion for culture when the sputum is negative; questions concerning differential diagnosis; and routine examinations before pneumothorax, thoracoplasty, pulmonectomy or lobectomy is carried out. The only contraindications are a deeply debilitated patient and extensive laryngeal tuberculosis.

Maier[19] reports a case in which transthoracic removal of a calcified lymph node caused hemoptysis by bronchial erosion. He states that bronchoscopic removal of a calcified lymph node that is eroding into a bronchus is feasible when the involved bronchus is endoscopically accessible and a sufficient portion of the broncholith projects into the lumen to enable one to grasp the object with an instrument. In his patient, however, since the site of bronchial ulceration was not accessible endoscopically, transthoracic surgical removal of the calcified lymph node was performed.

Packard[20] describes a patient with bilateral tuberculous bronchostenosis. No previous similar case has been found in the medical literature. In the case reported roentgenograms of the chest were normal throughout the period of observation. The early use of antimicrobial agents may prevent the development of increasingly severe stenosis and of parenchymal spreads. Moreover, plastic surgical repair of progressively severe bronchostenosis may be considered in cases exhibiting inactive or no parenchymal disease.

Mascher and Mattson[21] treated 22 patients with tracheobronchial tuberculosis with streptomycin. Bronchoscopic examination showed that healing of the local process occurred in 17 patients. Three patients were improved, and treatment failed in 2. Fibrotic stenosis developed in 5.

Laff, Hurst and Robinson[22] have studied the effect of bronchial involvement in primary tuberculosis of childhood. They conclude that bronchial involvement in the pathogenesis of parenchymal consolidation and in the course of primary tuberculosis in children is an important and frequently overlooked factor. Bronchoscopic treatment should be given not only to patients presenting evidence of wheezing, atelectasis or obstructive emphysema but also to every patient with childhood primary pulmonary tuberculosis whose progress is not considered satisfactory; the relative ease and safety of bronchoscopic examination in such patients, as well as some of the complications found in later life that might be averted, is stressed.

Radner and Snider[23] report 2 cases of paralysis of the recurrent laryngeal nerve as a complication of pulmonary tuberculosis. In both cases a dense mass, presumably caseous, developed in the region of the aortic arch, and marked apical retraction of the left-upper-lobe bronchus ensued. In both cases bronchiogenic carcinoma complicating tuberculosis was considered but was excluded by bronchoscopic and cytologic study.

Gebauer[24] describes the three-stage tracheobronchial reconstruction for tuberculous stenosis. Planigrams and bronchoscopy revealed beginning stenosis of the midtracheal third and the entire left main bronchus, in addition to almost complete occlusion of the right intermediate bronchus by a healed stenosis. In the first stage the trachea was opened, and a long, cane tube inserted. In the second stage the left bronchus was repaired with wire-supported dermal graft. In the third stage the trachea was repaired, the right middle and lower lobes removed, and a short tracheal tube inserted; the short tracheal tube was permanently removed two weeks later.

Foreign Bodies in the Tracheobronchial Tree

Percell, Mills and Schmidt[25] studied a case of subcutaneous emphysema complicating the aspiration of a foreign body. In considering the mechanism of this situation, they state that the foreign body produces increases in the intrapulmonary pressure and that air passes from the alveoli into the interstitial tissue of the lung either through a demonstrable tear in the wall or through the apparently intact membrane. These tiny bubbles coalesce to form larger ones and move in a stream along the perivascular spaces toward the mediastinum. Once air has reached the mediastinum, it escapes by three main routes: upward along the great vessels into the neck or through the weak spots in the mediastinum into the intrapleural spaces producing pneumothoraces or downward along the periesophageal areolar tissue into the retroperitoneal region. Therefore, after the aspiration of a foreign body, air in the subcutaneous tissues is an external indication that mediastinal emphysema is present and should be a warning that more serious complications, such as pneumothorax and compression of the great veins, may develop.

Kugelmass[26] reports 6 cases in which aminophylline administered by rectum had a sufficient relaxing effect on the bronchial or esophageal musculature to result in the dislodging of foreign bodies inspired or swallowed by children.

Benign Tumors of the Bronchus

In a collective review on the subject of benign endobronchial tumors, Langston[27] did not include bronchial adenomas in any detail because of the fact that they are not universally considered to be benign. He states that specific and clearly accurate information about all benign endobronchial tumors seems disappointingly meager. On the basis of histogenesis, these endobronchial tumors may be classified into epithelial and mesenchymal types. The epithelial tumors are by far the most common and are preponderantly malignant. Even the tumors catalogued under a benign heading (adenoma) are subject to serious suspicion. A few malignant mesenchymal tumors (sarcomas) have been reported, but it is the group of endobronchial tumors of mesenchymal origin and benign histology that medical writing has in effect designated as reliably benign. Critical appraisal of this mass of literature, however, reveals it to be confused, sketchy and even at times possibly inaccurate, casting an aura of skepticism around the behavior pattern of some of these tumors. They are prone to be of complex histologic composition and do not seem to merit guileless trust.

Prior and Jones[28] discuss the clinical and pathological features in 8 new cases of an unusual type of pulmonary neoplasm. Evidence is presented that these tumors are relatively benign, resembling most closely the pattern seen in the carcinoid type of bronchial adenoma. In addition to their histologic structure, common features of these tumors were their minute size, accidental discovery on microscopical examination, subpleural location and overwhelming predilection for females. The concomitant occurrence of bronchiectasis in the majority of the recorded cases suggests that the condition may be a factor in the pathogenesis of this atypical type of epithelial-cell proliferation.

Som and Feuerstein[29] report 2 cases of benign pedunculated lipoma of the bronchus in men fifty-five and fifty-nine years of age. One patient had had recurrent pneumonia for fifteen years, and the other had had a chronic cough for several years. Both had hemoptysis. Roentgenograms of the chest indicated the presence of bronchial obstruction, with atelectasis and infection. The lipomas were removed endoscopically, and the patients have remained symptom free. These cases emphasize the fact that, even after long-standing infection with bronchial obstruction, improvement or restitution to normal can be expected in the affected lobe if the patency of the bronchus is re-established. There is no indication for lobectomy in cases of this kind, but when lipomas occur in the pulmonary parenchyma, removal of the lung may be necessary for cure.

Carcinoma

Graham[30] believes that there is no doubt that the incidence of bronchiogenic carcinoma has shown a great increase in recent years. By contrast, the incidence of carcinoma of the stomach seems to be nearly stationary. In several large hospitals in the United States bronchiogenic carcinoma has passed cancer of the stomach in frequency. The evidence accumulated in both Great Britain and the United States indicates strongly that cigarette smoking is an important etiologic factor. Graham considers the cigarette cancer to be the epidermoid variety and different from the adenocarcinoma in pathogenesis.

Doll and Hill[31] also believe that there is a specific association between carcinoma of the lung and smoking; 1732 patients were studied.

Levin, Goldstein and Gerhardt[32] studied 1045 male patients with cancer, with particular attention to the occurrence of lung and lip cancers among the users of cigarettes, pipes and cigars. There were 236 patients with cancer of the lung. The data indicate that cancer of the lung occurs more than twice as frequently among those who have smoked cigarettes than among other smokers or nonsmokers of comparable age.

Baetjer[33] discusses the incidence of pulmonary carcinoma in chromate workers. The number of deaths due to cancer of the lungs and bronchi is greater in the chromate-producing industry than would normally be expected.

Muntean and Amon[34] studied the relation between pulmonary tuberculosis and carcinoma in 86 cases of pulmonary and bronchial carcinoma, 9 of which were associated with active pulmonary tuberculosis. In 5 of these there was no evidence of an etiologic relation between tuberculosis and neoplasm. In 4 other cases histologic examination revealed that the neoplastic process arose out of old tuberculous scar tissue.

Dotter, Steinberg and Holman[35] made angiocardiographic studies in 53 consecutive proved cases of pulmonary cancer. Angiocardiographic diagnosis of primary cancer of the lung was made in 34 of the 53 cases. The method is considered of sufficient value to be used routinely in the preoperative study of all cases of suspected cancer of the lung.

Pattison, Beck and Miller[36] reported 6 cases of bronchiogenic carcinoma with associated hypertrophic osteoarthropathy. In 5 of them hypertrophic osteoarthropathy was the first significant symptom, constituting a valuable early diagnostic finding in carcinoma of the lung.

Kaunitz[37] emphasizes the necessity for exploratory thoracotomy in carcinoma of the lung after negative bronchoscopy.

Abbott[38] presents his experience in attempting to extend the indications for resection in right-upper-lobe carcinomas. He suggests surgical resection of the carina, tracheal wall and contralateral bronchial wall in cases of total pneumonectomy.

Churchill et al.[39] studied 681 proved cases of carcinoma of the lung. Two hundred and ninety-four patients were subjected to thoracotomy, and a lobectomy or pneumonectomy was carried out in 171 (25.1 per cent of proved cases, and 58.2 per cent of those explored). One hundred and thirty-seven patients, 20.1 per cent of those in whom the diagnosis was established histologically, survived resection and left the hospital alive. There was a five-year survival rate of 20 per cent for the pneumonectomies (6 patients surviving five or more years), and of 25 per cent for lobectomies (4 patients surviving five or more years).

Ochsner and his co-workers[40] studied the frequency, diagnosis and early treatment of bronchiogenic carcinoma. Their comments regarding bronchoscopy are of interest:

> Early in our experience with bronchogenic carcinoma, bronchoscopy was thought to be the most valuable method of diagnosis, but it is now generally accepted that although bronchoscopy should be done in all instances, the percentage of carcinoma diagnoses made by this procedure is relatively small because most bronchogenic cancers are either in the periphery or in the upper lobe bronchi. Bronchoscopy should be done in every instance, however, not only because a biopsy study can be made of the lesions which are visible, but also because considerable information can be obtained by inspection of the trachea, carina, and the main stem bronchi, which may be of value in determining operability. However, in the present series, a diagnosis of carcinoma was made bronchoscopically in only 38% of the cases.

The results of treatment of bronchiogenic carcinoma are not as satisfactory as they should be because, in the 948 cases, only 59 per cent were operable, and 35 per cent were resectable; 28 per cent of patients survived resection, and only 6 per cent were alive at the end of five years.

Benedict's[41] experience with bronchoscopy in bronchogenic carcinoma has recently been reported as follows:

> [In his] personal experience with 2626 bronchoscopies, carcinoma was suspected in 848 cases. In these 848 cases 796 records were traced, and primary bronchogenic carcinoma was proved by various methods in 309 cases, or in 39 per cent of those in which it was suspected. Of the 309 proved cases bronchoscopic biopsy was positive in 189 cases (61 per cent) . . . . In addition to the likelihood of obtaining a positive biopsy in bronchogenic carcinoma, the experienced bronchoscopist can usually give an accurate opinion regarding operability or inoperability, particularly the latter. Carcinoma of the lung is almost certain to be inoperable, if (1) there is paralysis of one or both vocal cords, since this means that the tumor has invaded the recurrent laryngeal nerve; (2) the lesion is located above the level of the carina, because the trachea cannot be resected . . . [in rare cases parts of the tracheal wall have been excised]; (3) there is widening or fixation of the carina, because this means malignant invasion of the mediastinal lymph glands; (4) the bronchial tree itself is fixed, because in such cases the growth has invaded vital extrabronchial and extrapulmonary structures. If none of these evidences of inoperability is present, and there are no other contraindications to surgery, exploratory thoracotomy should be performed. The lesion may still be found to be inoperable since vital structures well outside the range of the bronchoscopist's observation may have been invaded. Positive evidence is always more valuable than negative evidence, and positive evidence of inoperability is of greater value than is negative evidence of probable operability.

Aufses and Neuhof[42] present a follow-up study of minute carcinoma of the major bronchi. The report concerns 2 cases previously cited. Bronchoscopic specimens in both were reported as carcinoma. One patient had a pneumonectomy, and has remained well for six years (no carcinoma could be found in the resected lung). At operation on the second patient, no gross tumor was found, and bronchoscopy during the operation gave no evidence of disease. Therefore, only a lobectomy was performed. Subsequent bronchoscopic examination was also negative. Five years later, clinical symptoms appeared, and bronchoscopy revealed a carcinoma of the main bronchus of the lung previously operated on. The patient died six and a half years after the original diagnosis had been made. If the pathologist makes an unequivocal diagnosis of cancer on examination of a specimen removed from a major bronchus, the surgeon should perform a pneumonectomy even though no gross evidence of a malignant lesion is found at operation.

McDonald and his co-workers[43] have made extensive studies on the significance of cell types in bronchiogenic carcinoma. Their types include bronchiogenic small-cell carcinoma, bronchiogenic squamous-cell carcinoma, bronchiogenic adenocarcinoma and bronchiogenic large-cell carcinoma. They report a total of 849 cases. From a study of

these extensive statistics it appears that the only type without an extremely poor prognosis is squamous-cell carcinoma.

Alveolar-cell tumor or pulmonary adenomatosis, according to Good,[44] is a rare neoplasm that has attracted a great deal of interest in recent years because of its apparent multicentric origin from the cells lining the pulmonary alveoli, and because of its apparent morphologic similarity to a disease of sheep known as "jagziekte" or "Montana progressive pneumonia." Although bronchoscopic examination is seldom of value in identifying the lesion, material obtained through the bronchoscope, either as tissue for biopsy or as secretions from the bronchial tree, may, when examined microscopically, enable one to establish a definite diagnosis.

In 2 cases of pulmonary adenomatosis reported by Peterson and Houghton[45] bronchoscopic examination was negative in the first case, but in the second it showed displacement of the trachea and carina to the right, without evidence of endobronchial disease.

In a case of pulmonary adenomatosis presented by Kennamer[46] bronchoscopy revealed a minimal redness of the mucous membranes and a frothy exudate pouring from all orifices.

Davis and Simon[47] describe 5 cases of alveolar-cell tumor of the lung, in only one of which bronchoscopy was performed. In that case bronchoscopic examination revealed reddened mucosa, which was edematous and bled easily. Two subsequent examinations in the same patient demonstrated an area of granular tissue at the middle-lobe orifice that was friable and bled easily. Microscopical examination of a biopsy specimen showed chronic inflammation. The authors conclude that a positive diagnosis of alveolar-cell tumor can at present be made only by thoracotomy and biopsy of the lung. However, cytologic studies of the sputum may aid in diagnosis.

Cytologic Diagnosis of Pulmonary Cancer

It is not possible to review all that has been written regarding the cytologic diagnosis of cancer of the lung by examination of the sputum and by examination of secretions obtained at the time of bronchoscopy. Bronchoscopic biopsy, when it is obtainable, is undoubtedly the most reliable and most satisfactory method of making a diagnosis of bronchiogenic carcinoma. In peripheral tumors, however, bronchoscopic biopsy is not possible, and in such cases studies of sputum as well as bronchoscopically aspirated secretions should be made for cancer cells. The greatest accuracy results when these methods are combined.

Pulmonary Lymphoma

Benedict[41] reports 12 cases of pulmonary lymphoma, in all of which bronchoscopy was interesting and valuable for its possible negative evidence of an uninvolved tracheobronchial tree, thus permitting surgery, because of the rare intrinsic bronchial invasion, for the possible positive evidence of widening and fixation of the carina or deviation fixation and narrowing of parts of the trachea or bronchi by extrinsic pressure, and for the disclosure of a bronchiogenic carcinoma or other intrabronchial lesion in addition to the lymphoma.

Beck and Reganis[48] reviewed the literature on primary lymphoma of the lung and reported 1 case. Bronchoscopy was carried out in 6 of 15 patients reviewed. In 3 it was reported to be normal. In 1 it disclosed suppuration in the affected lobe. In another it showed a narrowing and distortion of the bronchus in the affected area. In only 1 case was the tumor revealed and a positive biopsy taken.

Efskind and Wexels[49] have reported 3 cases of Hodgkin's disease of the lung with cavitation, in the first 2 of which bronchoscopy was negative. In the third bronchoscopy showed some broadening of the carina and purulent secretion in the right-upper-lobe bronchus.

Higginson and Grismer[50] describe a case of obstructing intrabronchial Hodgkin's disease in which bronchoscopy and biopsy established a diagnosis of Hodgkin's disease involving bronchial mucosa with squamous metaplasia of the epithelium. They believe that routine bronchoscopy in all cases of Hodgkin's disease, even without clinical evidence of bronchial obstruction, might prove of value diagnostically, therapeutically and statistically. Twenty-eight references to the literature are given.

Sarcoma

Giacomelli[51] reported a case of pulmonary sarcoma in which bronchoscopic examination revealed some stenosis and rigidity of the superior left bronchus. Biopsy was not performed. Surgery was carried out, but the patient died on the operating table. Autopsy disclosed spindle-cell sarcoma.

Metastatic Carcinoma of the Bronchus

Seiler, Clagett and McDonald[52] have discussed pulmonary resection for metastatic malignant lesions. They report 52 cases in the literature in addition to the records of 10 cases at the Mayo Clinic in which pulmonary resection was performed for metastatic malignant lesions. The primary tumor was sarcoma in 32 per cent (18 cases) and carcinoma in 68 per cent (39 cases) of the 57 cases in which the type of primary tumor was mentioned. The primary tumors for which resection of solitary pulmonary metastatic lesions was most frequently done were carcinoma of the large bowel (11 cases), hypernephroma (7 cases), fibrosarcoma (7 cases) and carcinoma of the ovary (5 cases). Bronchial involvement was noted in 63 per cent of the cases in which the reports especially mentioned this feature, or in 27 per cent of the entire group. The true percentage probably lies somewhere between

these two figures, indicating that in a substantial proportion of cases the tumor will be found to be invading a major bronchus. This is in contradistinction to the former teaching that bronchial invasion by a metastatic tumor is uncommon. A positive diagnosis was made by means of bronchoscopic biopsy in 16 per cent of the entire series.

Lambert[53] describes a case of removal by lobectomy of an adenocarcinoma of the upper lobe of the left lung and of a solitary metastasis to the right lung occurring fourteen and a half months later. The patient was still living and well six years and five months after the first lobectomy and five years and two months after the second lobectomy for the metastatic lesion.

Tumors of the Trachea

Evans[54] reports a case of a large benign tracheal neoplasm — a myxochondroma — surgically removed. Repair of the tracheal defect was undertaken successfully by incorporation of a full-thickness skin graft re-enforced by a stainless-steel wire.

Cahan[55] discusses a case of carcinoma of the trachea, with excision and repair of the defect with tantalum-mesh gauze and fascia lata. The patient was alive and without evidence of disease or change in the size of the tracheal lumen sixteen months after operation.

Gebauer[56] states that surgical repair of the tracheobronchial tree is a new field with a satisfactory experimental foundation and a promising, if not voluminous, clinical background. Lesions suitable for bronchial reconstruction may result from trauma, new growth or the healing of tracheobronchial tuberculosis. Five of 7 cases of successful bronchial resection with anastomosis or repair are briefly reported to illustrate the usefulness of this technic in salvaging undamaged pulmonary lobes or segments. When the tracheobronchial lesion is favorable, this procedure is preferable to the use of wire-supported dermal grafts. The two methods together provide a good means of tracheobronchial reconstruction and pulmonary salvage applicable to most of the deformities likely to be encountered, including obstructive lesions of the thoracic air passages heretofore regarded as therapeutic enigmas.

Bronchial Rupture

Scannell[57] reports the case of a ten-year-old boy who was hit by an automobile and sustained a closed injury with tension pneumothorax. It was necessary to do an immediate thoracotomy on the right, with resultant relief. A large bronchial tear was found and closed. Laceration of the upper and lower lobes was present; a portion of the former was nearly sheared off, and was resected. All tears were closed, and recovery was complete. The author states that a closed injury to the chest rarely results in bronchial rupture, and no record could be found in which operation had been done for its relief.

(To be concluded)

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MEDICAL INTELLIGENCE

APRESOLINE INTOLERANCE WITH BLADDER PARALYSIS

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A CASE of bladder paralysis in a fifty-eight-year-old woman who was taking Apresoline (1-hydrazinophthalazine hydrochloride) was recently reported by Goldstein et al.‡ The patient had had a surgical operation involving the bladder, and although there was no apparent connection between the operation and the paralysis, it seems desirable to present another case to help establish whether the disturbance was actually due to Apresoline.

Case Report

A 68-year-old woman was admitted to the hospital suffering from mild hypertensive cardiac failure. During a week's rest in bed the average blood pressure was 220/90, and it was decided to treat her with Apresoline by mouth beginning with 25 mg. every 6 hours. About 2 hours after the 2d dose the patient felt ill, shivered and was found to have a pulse rate of 120 per minute. She recovered in an hour. Unfortunately, this episode occurred in the middle of the night and the blood pressure was not measured, but the next morning it was 200/90 and in the afternoon it fell to 140/75 and then returned to normal (Fig. 1). About 36 hours after starting to take the Apresoline the patient had lost the ability to micturate voluntarily and did not regain it until 24 hours after the drug had been withdrawn, a total period of nearly 4 days. Bladder sensation remained unaffected. She had never had bladder trouble before. The drug was not withdrawn at once, since it was hoped that the difficulty in micturition would pass off as some other toxic effects do. Nausea and vomiting then developed and the patient had her first anginal attack. The administration of Apresoline was therefore stopped. The patient had also been completely constipated while taking Apresoline.

After 6 days' rest a single dose of 25 mg. of Apresoline was given by mouth, and in 45 minutes the blood pressure fell from a resting level of 220/80 to 185/70, where it remained for 25 minutes, with no significant tachycardia. Regular medication was then resumed more cautiously (Fig. 1), but the drug had to be withdrawn because of the severity of the side effects, which included headache, malaise, weakness, nausea and vomiting.

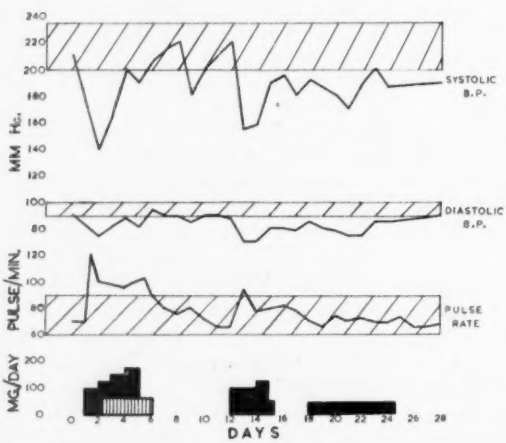

Figure 1. *Effect of Apresoline on Blood Pressure, Pulse and Bladder Function.*

The upper hatched area indicates the range of the systolic pressure and the middle hatched area the range of the diastolic pressure during a control period. The lower hatched area represents the range of the pulse rate during the control period. Apresoline dosage is shown by the solid areas, and the duration of bladder paralysis in the first course of the drug by the vertically hatched area.

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‡Goldstein, M. R., Schloss, W. A., and Cohn, S. H. Bladder disturbance due to Apresoline. *New Eng. J. Med.* **247**:525, 1952.

After a short interval another attempt to give the drug was again followed by side effects, and though these were only mild the patient was unwilling to have the dose raised in view of her previous experience. The drug was therefore abandoned. There was no difficulty with micturition during the 2d and 3d courses.

Discussion

Goldstein and his associates found a severely hypotonic bladder in their case, and it seems that Apresoline is capable of causing bladder paralysis by an unknown mechanism, for the drug is not thought to be a ganglion-blocking agent. The patient recovers from the paralysis spontaneously. Constipation was marked in the case reported above but cannot be definitely attributed to the drug.

The other side effects that compelled withdrawal of the drug are well known to occur with Apresoline.

Summary

A case of intolerance to Apresoline is reported. An unusual feature was the development of bladder paralysis, which did not recur when smaller doses were subsequently used. In view of a previous case report this paralysis is attributed to Apresoline.

We are indebted to Professor E. P. Sharpey-Schafer for permission to report this case.

DICKENS AND THE HOSPITAL FOR SICK CHILDREN

PROBABLY few of those who are familiar with the splendid edifice that today houses the Hospital for Sick Children in Great Ormond Street, London, are aware of the interest taken in it by Charles Dickens in the first few years of its existence.

The hospital was opened in 1852, in which year, with 32 beds, it cared for 143 inpatients and 1250 outpatients. In 1867 — probably not for the first time — there was printed, as a small pamphlet, the "Speech of Charles Dickens, Esq., as chairman at the Dinner on Behalf of the Hospital for Sick Children, Feb. 9, 1858." The editors are indebted to Dr. James L. Gamble for the privilege of examining this article. "The liberal response to this appeal," according to a statement made by the Committee, enabled it "to increase the number of beds for In-patients from thirty-two to forty-four. In the summer of 1865 additional wards were opened, and the number of Inpatients increased to 75."

The following excerpt from the speech made at that time by the author of *The Old Curiosity Shop* suggests the reason for his apparent success in obtaining funds for the enterprise:

> Some years ago, being in Scotland, I went with one of the most humane members of the humane medical profession, on a morning tour among some of the worst-lodged inhabitants of the old town of Edinburgh. In the closes and wynds of that picturesque place — I am sorry to remind you what fast friends picturesqueness and typhus often are — we saw more poverty and sickness in an hour than many people would believe in a life. Our way lay from one to another of the most wretched dwellings — reeking with horrible odours — shut out from the sky — shut out from the air — mere pits and dens. In a room in one of these foul places, where there was an empty porridge-pot on the cold hearth, with a ragged woman and some ragged children crouching on the bare ground near it — where, I remember as I speak, that the very light, reflected from a high damp-stained and time-stained house wall, came trembling in, as if the fever which had shaken everything else there had shaken even it — there lay, in an old egg-box, which the mother had begged from a shop, a little feeble, wasted, wan, sick child. With his little wasted face, and his little hot worn hands folded over his breast, and his little bright attentive eyes, I can see him now, as I have seen him for several years, looking steadily at us. There he lay in his little frail box, which was not at all a bad emblem of the little body from which he was slowly parting, — there he lay quite quiet, quite patient, saying never a word. He seldom cried, the mother said; he seldom complained; 'he lay there seeming to woonder what it was a' aboot.' God knows I thought, as I stood looking at him, he had his reasons for wondering — reasons for wondering how it could possibly come to be that he lay there, left alone, feeble and full of pain, when he ought to have been as bright and as brisk as the birds that never got near him — reasons, for wondering how he came to be left there, a little decrepit old man, pining to death, quite a thing of course, as if there were no crowds of healthy and happy children playing on the grass under the summer's sun within a stone's throw of him, as if there were no bright, moving sea on the other side of the great hill overhanging the city; as if there were no great clouds rushing over it, as if there were no life, and movement, and vigour anywhere in the world — nothing but stoppage and decay. There he lay looking at us, saying in his silence, more pathetically than I have ever heard anything said by any orator in my life, 'Will you please to tell me what this means, strange man? and if you can give me any good reason why I should be so soon so far advanced upon my way to Him who said that children were to come into His presence, and were not to be forbidden, but who scarcely meant, I think, that they should come by this hard road by which I am travelling — pray give that reason to me, for I seek it very earnestly, and wonder about it very much' and to my mind he has been wondering about it ever since. Many a poor child, sick and neglected, I have seen since that time in this London; many a poor sick child I have seen most affectionately and kindly tended by poor people, in an unwholesome house and under untoward circumstances, wherein its recovery was quite impossible; but at all such times I have seen my poor little drooping friend in his egg-box, and he has always addressed his dumb speech to me, and I have always found him wondering what it meant, and why, in the name of a gracious God, such things should be!

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39111

PRESENTATION OF CASE

A sixty-three-year-old woman was admitted to the hospital because of a "catch in her neck" on breathing.

The patient was well until five years before admission, when she had pneumonia, with fever, cough, shortness of breath and right-sided pleurisy. A roentgenogram showed a lesion that cleared on subsequent films. She had never felt well since that time, and had lost a total of 20 pounds though her appetite had remained good. Persistent cough, worse in the mornings, was present, and had become increasingly productive of moderate amounts of greenish-yellow sputum, with rare streaks of blood. Dull chest pain, usually bilateral, was present intermittently and was exaggerated by coughing. One year before admission she noted the sensation of a "lump in the throat" that was bothersome but did not interfere with swallowing. For the past five months difficulty in breathing, principally inspiratory, had increased markedly, to the point of respiratory distress. Orthopnea requiring three pillows for relief had developed but was intermittent. There was no peripheral edema. Six weeks before admission she noted persistent hoarseness and an abrupt increase in the choking sensation associated with cough. She had visited several doctors and had received a variety of antibiotics without relief. A "blood test" at another hospital had been reported positive seven weeks previously.

The past history was noncontributory. She had no knowledge of previous venereal disease.

Physical examination revealed a well developed and well nourished woman, appearing chronically ill, with marked inspiratory and expiratory stridor exaggerated by cough, which was almost continuous. The thyroid gland was slightly enlarged, and there was questionable deviation of the trachea to the right. There was limited motion of the chest. There were hyperresonance and relatively diminished breath sounds at the lung bases. Harsh and greatly accentuated breath sounds were heard throughout both lungs, being especially loud and harsh over the trachea anteriorly. No rales were present. The heart was normal. There was a small umbilical hernia and a ++ cystocele.

The temperature was 98.6°F., the pulse 80, and the respirations 20. The blood pressure was 130 systolic, 80 diastolic.

The urine had a specific gravity of 1.010, and was otherwise normal. Examination of the blood revealed a red-cell count of 4,010,000, with a hemoglobin of 12.6 gm. per 100 cc., and a white-cell count of 13,600, with 55 per cent neutrophils, 42 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. A blood Hinton test was "doubtful." The blood nonprotein nitrogen was 33 mg., and the fasting blood sugar 95 mg. per 100 cc. A roentgenogram of the chest showed the heart to be within normal limits. Pulmonary vessels were not engorged, and there was no evidence of mediastinal adenopathy. Scattered discrete parenchymal calcifications and some linear scarring were present in the right middle and lower lung fields. There was a suggestion of dilated bronchi in the right lower lung field. There was no evidence of active pulmonary disease. The diaphragm was low, and its motion greatly limited, probably owing to emphysema. There was marked narrowing of the upper trachea just below the larynx, but the extent and character could not be determined. Barium-swallow examination demonstrated normally functioning pyriform sinuses and pharynx, with no obstruction to swallowing or deviation of the esophagus. Laryngoscopic examination revealed complete paralysis of the left vocal cord, with fixation in the midline.

The patient's condition remained unchanged, and on the fifth hospital day a bronchoscopy was performed. The left-vocal-cord paralysis was confirmed. The immediate subglottic area was clean. About 1.5 cm. below the vocal cords, the tracheal lumen was narrowed circumferentially, apparently by a submucosal mass that bulged into the lumen. The mucosa over it was smooth, firm and nonfriable. The mass extended for 3 or 4 cm. down the trachea. Beyond the protrusion the trachea in its lower half appeared fairly normal. The carina was blunt. There were secretions in both main bronchi, but all subdivisions were patent. There was no inflammation or ulceration. A biopsy was taken.

DIFFERENTIAL DIAGNOSIS

DR. LAMAR SOUTTER*: I should like to see the x-ray films.

DR. JOHN F. GIBBONS: The films made shortly after admission show emphysematous lung fields, increased anteroposterior diameter of the chest, a

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low diaphragm and widened intercostal spaces. In the right lung field there are discrete calcified areas of linear scarring, probably the result of an old inactive process. The heart is small; the aorta is not remarkable. The esophagus apparently is not deviated, but the trachea appears to be narrowed for several centimeters. In the lateral view the trachea is not well outlined; by fluoroscopy it was the impression that it was narrowed. The presumption was that the narrowing was due to a thyroid gland extending down from the neck although I can see no evidence of a thyroid mass below the sternum.

DR. SOUTTER: Can you see any calcification in the trachea in the region of the narrowing?

DR. GIBBONS: I cannot.

DR. SOUTTER: When she had the barium swallow, how did the esophageal mucosa in the region of the tracheal lesion appear?

DR. GIBBONS: It was not mentioned, and I assume that it appeared to be normal — in other words that the barium did not cling to it in an irregular fashion.

DR. SOUTTER: Let us review briefly the positive findings. The patient apparently had a partial obstruction of the upper trachea caused by a mass exterior to the bronchial mucosa. The bronchial mucous membrane at the time of the bronchoscopy was said to be intact. She had cough, sputum, orthopnea and respiratory distress, which tend to indict the lung. She also had evidence of calcification and fibrosis in the lung, which makes one think of an old tuberculous process. She had some evidence of emphysema.

Must I think of two diseases causing the symptoms, one involving the upper trachea and one involving the lungs? Or can I concentrate my attention on one lesion only? The absence of sufficient pulmonary or cardiac disease to account for the difficulty with breathing and cough, the lack of peripheral edema and extensive fibrosis and the normal size of the pulmonary arteries make me believe that the symptoms did not result from pulmonary disease. The heart was not enlarged, nor was there evidence of pulmonary edema. These negative findings suggest that there was no abnormality of the heart.

There was no history of asthma. The orthopnea is quite interesting in that it was intermittent. When orthopnea is associated with an obstruction in the airway, the patient notices that it is easier to breathe when sitting up. Such a patient, however, can breathe perfectly well when lying down if she can control her fears of strangulation. Dyspnea, which is caused by diminished lung function, however, is made worse by lying down, and hence is rarely intermittent.

The cough and increased secretions could have been caused by extrinsic narrowing or deviation of the trachea. The fact that the sputum was streaked with blood is probably of no particular significance because the patient was coughing hard and persistently. We have seen this type of syndrome in patients with a marked deviation of the trachea after a pneumonectomy. Sometimes such patients have constant cough and raise secretions that may be blood tinged. Hence I believe that all the symptoms are perfectly consistent with a lesion in the upper trachea. Let us proceed, therefore, to the diagnostic possibilities of such a lesion.

There are a number of conditions to consider, the first of which is an inflammatory process. The doubtful blood Hinton test, in addition to a positive one at another hospital, suggests syphilis. Most of us do not often see syphilis of the lung because the public-health and therapeutic measures of preceding medical generations have almost eliminated it. When syphilis of the respiratory tract occurs, it is more commonly in the trachea than in the pulmonary parenchyma. It occurs as a gumma. A gumma would involve the mucous membrane; it is quite obvious from the bronchoscopic findings on the patient under discussion that the mucous membrane was not involved. Furthermore, cough was present for a long time, probably for five years, and certainly for one year. During the course of that time she must have been given a number of expectorants, most of which usually contain iodides. She probably received enough iodine to resolve a gumma of the trachea, and yet the lesion grew steadily worse. The doubtful blood Hinton test does not signify anything. The Hinton test is a very sensitive one. A doubtful test is simply an indication to the physician that he should study the patient further to determine whether or not the patient has syphilis. In the blood bank of this hospital many doubtful Hinton tests are found on donors who are subsequently proved to be free of the disease. I can therefore exclude syphilis as a cause of this patient's trouble.

The disease in the lung does not look like active tuberculosis, nor was there bacteriologic evidence of it. Furthermore, active tuberculosis involving the trachea or a bronchus causes inflammation and ulceration, neither of which was present, according to the bronchoscopy note. Other infectious processes can be eliminated on the same grounds. The lack of an inflammatory process in the mucous membrane makes me believe that they are not likely diagnostic possibilities.

Next, I must consider cancer involving the trachea, the first and commonest of which is a primary bronchogenic carcinoma. Any lesion that can occur in the bronchus can also occur in the trachea but will do so with less frequency; hence all types of bronchogenic carcinoma must be considered. The commonest of these is the squamous-cell carcinoma. The presence of such a lesion would explain some of the symptoms. It would account for invasion of the left recurrent laryngeal nerve.

Squamous-cell carcinoma spreads very early through the lymphatics to the local lymph nodes, but the patient had no local lymph-node enlargement in the neck. It is primarily a rapidly growing lesion. Such a lesion in the trachea should give definite evidence of destruction of the mucous membrane by tumor after a few months of growth, and yet the bronchoscopist saw none.

The other types of highly malignant tumors that occur in the mucous membrane and in the bronchial wall of the trachea are the adenocarcinoma, the oat-cell carcinoma and the undifferentiated carcinomas. Again, the lack of involvement of the mucous membrane, the absence of enlarged lymph nodes in the neck and the history of the slow growth of this process render these tumors unlikely diagnostic possibilities.

What about secondary tumors? That suggests two types of possibilities: invasive tumors arising in organs that lie in close proximity to the trachea and metastases from distant tumors. The thyroid gland is a logical site of origin of an invasive tumor. Thyroid cancer can be divided into the slowly growing tumors, including adenocarcinoma and adenoma, and the rapidly growing anaplastic tumors. All these tumors can be invasive. If they invade the trachea, they usually do so through all layers, and yet in this case there had been a lesion growing into the trachea for a long time but the mucosa remained intact. Also, there was no evidence of spread to the regional lymph nodes. That, again, is inconsistent with the usual behavior of thyroid cancer. The rapidly growing tumors of the thyroid gland and most of the slowly growing ones, with the exception of some of the very small adenomas, usually manifest themselves by a markedly enlarged gland, but the thyroid gland in the case under discussion was not markedly enlarged so far as we can tell.

Could a colloid goiter have caused this picture? It can certainly distort the trachea, but it does not invade the tracheal wall and rarely causes recurrent-laryngeal-nerve paralysis. It is therefore most unlikely that a thyroid cancer or goiter had caused this woman's symptoms.

Should I consider a parathyroid tumor? Most parathyroid tumors give systemic evidence of parathyroid disease; such evidence was lacking. They can become invasive, but rarely do so.

A tumor of the esophagus is also a possibility. The primary ones arising in the mucous membrane are squamous-cell carcinoma and adenocarcinoma. The commonest symptom of these carcinomas is dysphagia. Usually, roentgenographic study of the mucous membrane shows irregularity fairly early in the disease. Any such tumor that is extensive enough to invade the trachea should be readily detectable in the esophagus. It is safe, therefore, to exclude these tumors.

There are other relatively rare tumors of the esophagus that have to be considered. The benign ones are leiomyomas, fibromas and neurofibromas. They characteristically remain beneath the mucous membrane and in the esophageal muscle in which they arise. They cause distortion of the mucous membrane, with swallowing difficulty, long before they disrupt through the muscle coat of the esophagus. In this hospital, of the 22 benign intramural tumors we have seen, only 2 have protruded through the muscle. One was a polypoid growth that caused no symptoms, and the other one surrounded the esophagus, became calcified and interfered materially with swallowing. The symptoms they caused were primarily esophageal. It would be extremely unlikely for such a tumor to invade the recurrent laryngeal nerve. The malignant intramural tumors of the esophagus are fibrosarcoma, leiomyosarcoma, rhabdomyoma and, occasionally, a lymphoma that has its primary focus in the esophagus. These tumors can invade surrounding structures, but all that I have been able to find in the literature and in this hospital, of which there are 3, ulcerated the esophageal mucous membrane, so that I think they are unlikely to have been present in this patient.

Metastasis from a distant organ is a possibility, but extremely rare.

I come, therefore, to the primary benign tumors arising in the trachea itself. These tumors, which are fairly rare, are papillomas, fibromas, chondromas, hamartomas, osteomas and various forms of lipomas. These benign tumors have two characteristics in common that are important in this discussion. The first is that they usually protrude into the lumen of the trachea as polypoid growths. The second is that they are not invasive. In other words, they would not be likely to involve the recurrent laryngeal nerve. On that basis I can say that they are unlikely diagnostic possibilities in this case.

I must still consider the tumors of low-grade malignancy that can arise in the bronchi or trachea. These are of two types, the basal-cell carcinoma, an extremely rare tumor that usually arises as a submucosal polypoid growth and is not locally invasive (at least the 2 cases we have had in this hospital were not), and the adenoma. The adenomas are of two types, the carcinoid and the cylindroma. They are fairly common tumors compared with those I have mentioned so far. They occur equally in men and women. Although they usually appear in persons younger than this patient, we have removed one from a man of seventy-six. They can be locally invasive, particularly the cylindromas. They occur in a ratio to carcinoma of 1:10, according to Dr. Edward D. Churchill. Eighty to 90 per cent of the cylindromas extend beyond the cartilaginous wall of the trachea or into the surrounding tissues. They may protrude into the lumen of the trachea, but they remain beneath the mucous membrane, a very important diagnostic point in

this case. They are slow growing and slow to metastasize, particularly if they remain encapsulated. One, a cylindroma that we excised about four years ago in this hospital, occurred in the cervical trachea. It caused vocal-cord paralysis and invaded the thyroid gland.[1] In that case the diagnosis was made from the thyroidectomy specimen.

Despite the number of diagnostic possibilities in this case, I should like to offer as a diagnosis that this was an adenoma of the trachea of the cylindromatous type.

Dr. Edward B. Benedict: What do you mean by an adenoma? Do you call a cylindroma an adenoma?

Dr. Soutter: Dr. Ronald C. Sniffen and I have gone over the cases of adenoma in this hospital. He has classified them into the carcinoid and the cylindromatous types. There is a great deal of discussion in the literature about adenomas, but I think that most people would consider a cylindroma as a form of adenoma.

Figure 1. *Opened Trachea, Showing Cut Edges of Tracheal Cartilages Surrounded by Tumor (Arrow Points to Submucosal Tumor).*

Dr. Benedict: I have never seen an adenoma that was not more or less a round mass that protruded into the lumen of the bronchus or trachea.

Dr. Soutter: Some of the adenomas in this hospital have protruded only slightly into the lumen.

Dr. Benjamin Castleman: I think that Dr. Soutter stated what most pathologists now believe[2]—that there are two types of adenomas of the bronchus or trachea, one the carcinoid type, which protrudes into the lumen as a polypoid mass much more often than the cylindromatous type, which is an elongated submucosal mass that protrudes somewhat but not as much as the carcinoid type. That is a generalization, but it holds true in most cases.

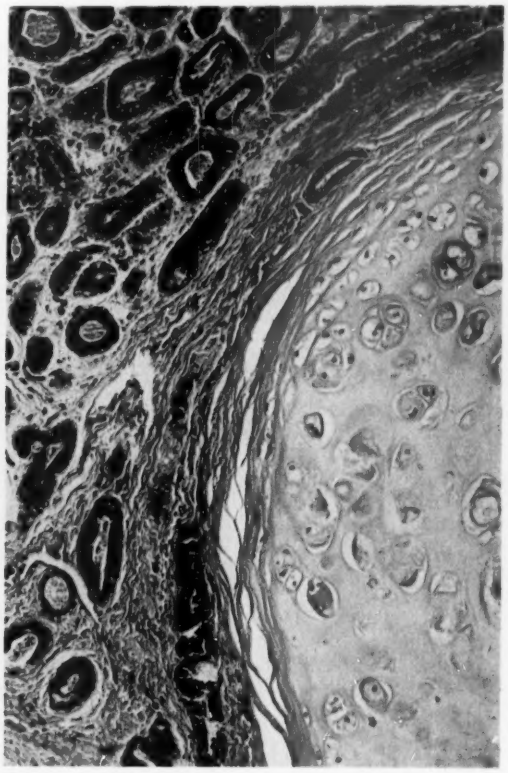

Figure 2.

Clinical Diagnosis

?Gumma.

Dr. Lamar Soutter's Diagnosis

Adenoma of trachea, cylindromatous type.

Anatomical Diagnosis

Adenoma of trachea, cylindromatous type.

Pathological Discussion

Dr. Castleman: The biopsy was done at the Eye and Ear Infirmary by Dr. E. W. Rice, who took a bit of the protruding submucosal mass. The biopsy

showed that it was a cylindroma or an adenoma of the cylindromatous type. After the biopsy there was a great deal of discussion about how the patient should be treated. It was believed that the mass was so long that it could probably not be entirely removed. A vitallium tube was inserted as a prosthesis, and the patient got along fairly well

FIGURE 3.

for a while. Then because the tube became plugged, the surgeon had to operate on the patient through a thoracotomy; during the operation there was cardiac arrest, and the heart had to be massaged. The patient lived for eight days after that in coma and finally died.

Autopsy showed a lesion in the trachea that at a cursory glance did not seem to be too striking. The tracheal wall to a point 2 cm. from the bifurcation was thickened, but the mucosa appeared intact. Raising the mucosa, however, were several nubbins, which upon cross section proved to be completely surrounding the tracheal cartilages (Fig. 1). This form of spread is typical of the cylindromatous type of adenoma, which is submucosal and is much more invasive than the carcinoid type. The carcinoid type is the one that protrudes as a polypoid mass into the lumen of the trachea although it may also extend through the wall. This photomicrograph shows the mucous secretion that is present in most of the cylindromatous type of adenomas and not present in the carcinoid type. Here is tracheal cartilage surrounded by tumor, which as a rule does not destroy the cartilage (Fig. 2). The cells are uniform and small and look perfectly benign; these tumors do not have any anaplasia or mitotic activity but are very slowly invasive. In this section, taken outside the trachea, is a nerve, probably a twig of the recurrent laryngeal nerve, completely surrounded by tumor (Fig. 3). A small part of the thyroid gland was also invaded by tumor.

DR. SOUTTER: The trachea has been resected here and in other hospitals in a number of cases. A metal tube has been successfully used in other cases as a prosthesis. Also, the tracheal stump has been brought out through the sternum as an alternative to a prosthesis. I think it was a very worthwhile attempt on Dr. J. Gordon Scannell's part; it is too bad it failed. Probably, the reason for the failure was the extent of the lesion.

DR. HELEN S. PITTMAN: I think that Dr. Soutter ought to be given an expression of professional appreciation. This was one of the best discussions I have heard.

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CASE 39112

PRESENTATION OF CASE

A fifty-year-old married woman was admitted to the hospital because of abdominal swelling.

Two months before admission the patient noted the onset of swelling of the abdomen associated with some nausea but no vomiting. For two weeks before entry she had experienced pain in the left lower quadrant of the abdomen and pain and a bearing-down sensation in the pelvis.

The patient had a history of "bronchitis" for many years and had been hospitalized several times because of pneumonia. Six years before admission she was found to have rheumatic heart disease with mitral stenosis and two years later was hospitalized because of congestive heart failure. She had also had an episode suggestive of pulmonary infarction for which bilateral saphenous-vein ligations were done three years before admission. She had been followed in the Rheumatic Fever Clinic and treated with digitalis and a low-salt diet. On this regimen there had been no signs of congestive heart failure for four years.

Physical examination showed a well developed and well nourished woman who was able to lie flat in bed with only a slight increase in respiratory rate. The neck veins were visible when the patient sat up but were not distended. The chest was clear to percussion; there were moist, crackling rales at both lung bases posteriorly. The heart was enlarged, the border of dullness extending to the anterior axillary line. There was a slow auricular fibrillation. There was an accentuated snapping mitral first sound, with a Grade 2 mitral diastolic rumble. The pulmonic second sound was greater than the aortic. The abdomen was tense with ++++ ascites. No organs or masses were palpable. There was no ankle edema.

The temperature was 98.6°F., the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

The urine had a specific gravity of 1.008 and was negative for albumin and sugar; the sediment contained a few white cells per high-power field. Examination of the blood showed a hemoglobin of 12.5 gm., and a white-cell count of 6900, with 76 per cent neutrophils, 20 per cent lymphocytes and 4 per cent monocytes. The nonprotein nitrogen was 24 mg., the total protein 6.93 gm., the albumin 3.49 gm., and the globulin 3.44 gm. per 100 cc. The prothrombin time was 13 seconds (normal, 13 seconds). A bromsulfalein test demonstrated 8 per cent retention of the dye, and a cephalin flocculation was ++ in twenty-four and +++ in forty-eight hours. A roentgenogram of the chest revealed the same findings noted about one year before entry. There was some blunting of both costophrenic angles and multiple densities in both lungs thought to be on the basis of hemosiderosis. The heart was enlarged.

During a diagnostic paracentesis 150 cc. of clear, dark-yellow fluid was removed. This had a specific gravity of 1.021 and contained 1200 red cells and 200 white cells per cubic millimeter, with 70 per cent lymphocytes and 30 per cent neutrophils. The total protein was 5.4 gm. per 100 cc. Cultures and smears for bacteria, including tubercle bacilli, were negative. On cytologic examination no malignant cells were found. Skin tests with old tuberculin, 1:100,000 and 1:10,000 dilution, were negative. Two days later 3000 cc. of murky-brown fluid was removed from the abdomen, examination of which revealed similar findings as before except that the differential white-cell count was 60 per cent neutrophils and 40 per cent lymphocytes. On physical examination at this time the abdomen was soft, without tenderness or masses. On pelvic examination an extremely tender, firm, but boggy mass, which moved with the uterus, was palpable in the posterior cul-de-sac. Peritoneoscopy was performed nine days later, when 2000 cc. of cloudy, yellow fluid was aspirated. The pelvic peritoneum had a slough-like appearance, with multiple yellowish lesions. The left tube was markedly inflamed and covered with yellowish slough. Just below it lay a firm, gray, semisolid, cystic mass, which was rounded and smooth surfaced and measured about 10 cm. in diameter. Other yellowish lesions were noted on the peritoneum as high up as the liver. A biopsy of one of the lesions was later reported by the pathologist as "purulent exudate." A plain film of the abdomen, a gastrointestinal series and a barium-enema examination were all negative.

While in the hospital, the patient continued to be nauseated but did not vomit. From the fifth hospital day on she had a fever, with daily temperature elevations to 101°F. associated with a leukocytosis, the white-cell count ranging from 12,000 to 15,000.

About a month after admission an operation was performed.

Differential Diagnosis

Dr. Jacob Lerman*: From the history we learn that the patient had rheumatic heart disease with mitral stenosis and auricular fibrillation, and one episode of congestive heart failure. The presence of ascites in such a patient could be due to several conditions, the most important ones being cardiac cirrhosis or mesenteric thrombosis after an embolus. Against the former is the absence of congestive heart

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failure before and during admission; against the latter is the absence of paralytic ileus and the fact that the patient was not too sick.

Laboratory data revealed slight liver damage as indicated by an abnormal albumin-globulin ratio and a +++ cephalin flocculation in forty-eight hours. The fluid in the abdomen was a clear exudate that subsequently became murky brown, probably as a result of bleeding after the first tap. The change from 30 to 60 per cent neutrophils in the abdominal fluid is consistent with the presence of blood in the peritoneal cavity. The negative tuberculin tests argue against a diagnosis of tuberculous peritonitis.

In general I must try to evaluate the presence of a tender mass in the posterior cul-de-sac, an exudate in the peritoneal cavity, evidence of pelvic inflammation and yellowish lesions involving the peritoneum. At this point let us see the x-ray films.

Dr. John F. Gibbons: A series of chest roentgenograms has been selected. In the first, made nearly five years before admission, the pulmonary segment of the cardiac shadow is accentuated, but there is no evidence of cardiac enlargement otherwise. The lung fields show diffuse exaggeration of the vascular shadows and multiple diffuse punctate densities, which are thought to be hemosiderin deposits in the lungs. Both costophrenic sulci are blunted, presumably by thickened pleura. Subsequent films made about a year and a half before and at the time of admission reveal a progressive decrease in the pulmonary vascular engorgement, but the stippling in the lung fields remains. The configuration of the heart is not detectably altered. These findings suggest disease of the mitral valves with hemosiderosis in a patient who had episodes of cardiac decompensation.

Dr. Lerman: Then from an x-ray point of view the degree of congestive heart failure had diminished.

Dr. Gibbons: That is correct. A film of the abdomen made shortly after admission shows a diffuse haze that is probably due to ascites.

Dr. Lerman: Are the liver and spleen enlarged?

Dr. Gibbons: No.

Dr. Lerman: Obviously, the diagnosis is not simple. I shall discuss it under the headings of infection, tumors and miscellaneous conditions. The most likely sources of infection, on a statistical basis, are the tubes and ovaries, or both. Chronic pelvic inflammation with acute exacerbation and rupture of a tube, or leakage of pus from a tube into the posterior cul-de-sac, could account for the major portion of the clinical findings. This diagnosis is also consistent with the findings at peritoneoscopy and by biopsy. However, negative cultures and smears throw some doubt on this diagnosis. The description of "yellowish lesions" involving the peritoneum as high up as the liver is also unusual in this condition.

Is this tuberculous peritonitis? The history and the physical examination are consistent with this diagnosis, but the negative smears and cultures and the negative tuberculin tests tend to rule this out. Other infections, such as actinomycosis, are a possibility, but the data are not sufficient to settle this point. Echinococcus cyst is a remote possibility, and the rupture of a cyst may produce ascites. However, the evidence for such a diagnosis is not available.

One should consider infections arising in an organ other than the pelvic organs. I have already mentioned peritoneal irritation associated with mesenteric thrombosis. A ruptured gall bladder may cause pus to accumulate in the posterior cul-de-sac, but the patient would undoubtedly have been much sicker and would have had paralytic ileus. Pancreatitis, particularly a subacute variety, would be more consistent with the clinical findings such as the ascites, the yellowish lesions and the mass in the pelvis. Certainly, the patient was not sick enough for an acute pancreatitis, and there was no history of a sudden onset. These findings are consistent only with a slowly developing, progressive pancreatitis.

In the category of tumors one must consider both the benign and malignant varieties. An ovarian fibroma is frequently associated with ascites. One variety of this is the Meigs-Cass syndrome,[1] in which the ovarian fibroma is associated with pleural effusion as well as ascites. The fluid in this case is usually a transudate. Moreover, this diagnosis does not account for the other findings in the peritoneal cavity, or for the stormy reaction during the hospital stay. Objections can also be raised against the diagnosis of malignant tumors of the ovary, some of which are associated with ascites. The absence of malignant cells in the fluid also argues against this diagnosis. Of the various malignant ovarian tumors pseudomucinous cystadenoma could simulate the clinical picture most closely. However, the character of the fluid is different and the biopsy of the peritoneal lesions is against such a diagnosis. A Krukenberg tumor from the gastrointestinal tract or ab-

dominal lymphoma, both of which may be associated with ascites, should be considered, but the evidence is against these diagnoses as it is against the other tumors.

In summary it seems that the diagnosis is either pelvic inflammation or subacute pancreatitis — I cannot be sure which is the more likely. It is conceivable that the infection originated in another organ, but I cannot find the evidence.

Dr. Edward B. Benedict: My impression from the peritoneoscopy was that the gross findings were not typical. My first choice was tuberculous peritonitis, and my second carcinoma. When the pathology report of "purulent exudate" came back I believed that both tuberculosis and carcinoma were probably excluded because in those diseases the accuracy of peritoneoscopic biopsy is high. I therefore strongly urged laparotomy.

Dr. Winfield S. Morgan: Dr. Shaw, will you give us the clinical impression on the ward, and describe your operative findings?

Dr. Robert S. Shaw: On the Surgical Service it was thought that this patient with a peritoneal exudate and a pelvic mass had a carcinoma of the ovary.

Clinical Diagnosis

Carcinoma of ovary.

Dr. Jacob Lerman's Diagnoses

?Pelvic inflammation.

?Subacute pancreatitis.

Rheumatic heart disease, with mitral stenosis and auricular fibrillation.

Anatomical Diagnosis

Fibroma of ovary.

Pathological Discussion

Dr. Shaw: At laparotomy there was a minimal inflammatory reaction in the pelvic peritoneum entirely consistent with previous paracentesis. None of the tubercle-like peritoneal lesions described at the peritoneoscopy were seen. The right ovary was found to lie in the cul-de-sac, to be firm and pale and to be enlarged to a diameter of approximately 10 cm., presenting the characteristic picture of an ovarian fibroma. The left tube and ovary appeared normal. The evacuation of approximately 3 liters of ascitic fluid and a bilateral salpingo-oöphorectomy were performed. The uterus was small and atrophic. There were numerous old adhesions of small bowel in the pelvis, but exploration of the remainder of the abdominal cavity was entirely negative.

Dr. Morgan: The specimen received in the laboratory was a large, roughly ovoid mass measuring 12 by 7 by 5 cm. and weighing 310 gm. This apparently had replaced the right ovary. The surface was smooth, glistening and tan gray; on section it was firm and yellow gray, with mottled areas of necrosis. Microscopically, multiple sections of the mass showed a similar picture of dense, interlacing bands of cellular fibrous tissue and collagen. The cells were ovoid or spindle shaped. The picture was typical of a fibroma.

It is well known that fibromas of the ovary may be associated with ascites[2] and in still other cases with ascites and hydrothorax, the latter being examples of the Meigs-Cass syndrome.[1] It is thought that the peritoneal fluid results not from peritoneal irritation by the tumor but by a transudation of fluid from the tumor itself. In cases of Meigs-Cass syndrome, the pleural fluid is apparently derived from the ascitic fluid by transmission through diaphragmatic lymph channels.[3]

Dr. Shaw: The ascites did not reaccumulate after operation, and except for mild menopausal symptoms, the patient had been doing quite well when seen on a follow-up visit four months after the operation.

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THE RIGHT TO DISAGREE

The president of Harvard University, reporting on his twenty years' stewardship before laying down his academic duties to become High Commissioner to Western Germany, had many matters on which to comment. His period in the University's history has been divided into three historic episodes: the Great Depression, the War against the Axis Powers and the first part, at least, of the Global Struggle with Russian Communism. He has seen the total student enrollment vary from a Depression figure of 8536 in 1932 to a war minimum of 1826 on January 1, 1944, and a Bill of Rights maximum of over 14,000 in 1947, which has dropped to the present figure of 10,200, the plan being to diminish it by another 1000. For the same period the gross expenditures of $13,807,000 in 1933 have risen to $14,085,000 in 1940 and $33,637,000 in 1951-1952. In this same score of years all the eight professional schools that have been in existence during the entire period, except those of dental medicine, education and law, have shown an increase in the student body, and all except the Divinity School, in their budgets. The Medical School, with a 165 per cent rise, has shown the largest increase of all in budget, except for the youthful School of Public Health, whose budget has gone up 329 per cent to keep pace with a student-body increase of 504 per cent and a 186 per cent enlargement of the staff.

But medical education is known to be painfully expensive; what is not generally known is that the graduate schools at Harvard are not fed from any common trencher, but must go far toward providing their own support. As President Sparks, whose administration ended just a hundred years ago, is said to have observed, "Each tub here at Harvard stands on its own bottom."

Regardless of their financial dependence or otherwise there is one form of independence that will be found in each department of the University, and that is independence of thought — the right to disagree. "It would be a sad day for the United States," Mr. Conant writes, "if the tradition of dissent were driven out of the universities. For it is the freedom to disagree, to quarrel with authority on intellectual matters, to think otherwise, that has made this nation what it is today."

Courage may be required to disagree when intellectual noncomformity is suspect and when freedom of thought is so easily confused with subversion, but it must be constantly remembered that those who seek to root out the open mind even as do the acknowledged enemies of freedom may be equally freedom's enemies.

This nation was founded by dissenters to whom the very idea of present-day Communism with its restriction of freedom would be abhorrent. Further words of Mr. Conant, however, show how finely the line may be drawn and how difficult it is to draw it:

> As I have said on more than one occasion in the past few years, I would not be a party to the appointment of a Communist to any position in a school, college or university. There are no known adherents to the Party on our staff and I do not believe there are any disguised communists either. But even if there were, the damage that would be done to the spirit of this academic community by an investigation by the University aimed at finding a crypto-communist would be far greater than any conceivable harm such a person might do.

And yet again:

> How to serve a free nation at a time of partial mobilization, how to reconcile the essential tradition of dissent with the need for national unity in the fact of danger — these are the major problems now facing this ancient community of scholars.

In 1929 another Harvard graduate, Justice Oliver Wendell Holmes "The Great Dissenter" wrote one of his last dissenting opinions:

> *If there is any principle of the Constitution that more imperatively calls for attachment than any other it is the principle of free thought — not free thought for those who agree with us but freedom for the thought that we hate.*

In times such as these through which the world now passes, there is only one possible way to reconcile the principles of freedom with the necessity for reasonable security — to maintain the tradition of dissent, but to guard first the rights and safety of even the smallest law-abiding minority.

THE INSTITUTE MOVES FORWARD

TEACHING is but one of the tools with which education is shaped, and it is with results rather than methods that the Committee on Postgraduate Education of the Massachusetts Medical Society and its Postgraduate Institute are ultimately concerned. Consequently, the effort to help the practitioner keep abreast of the advances in medicine must consist of something more than a mere display of those facts and technics with which he should be familiar, in the judgment of some presumably more sophisticated person.

A great deal more is necessary if an institute, which is "an organization to promote art, science, or the like, as a society, college or technical school," is to fulfill the broad purpose not only of giving the practitioner greater skills with which to treat his patients, but the capacity of finding greater intellectual and spiritual rewards in the use of these skills. For the practice of medicine is more than merely one of the learned professions; it is a way of life that gives its greatest rewards in the living of it.

The quick if not easy success of the Postgraduate Medical Institute and its rapid growth and popularity are matters of recent history. The Survey of Postgraduate Medical Education from which the Institute developed was launched in June, 1951, with a pilot teaching experiment the first year in Gardner. Otherwise it operated as a fact-finding mission to list the available opportunities for such education; this listing on a monthly and yearly basis has continued and is available on subscription.

The Institute itself was established in 1952 not only to continue the functions mentioned above but to organize and put in operation actual teaching — or better — learning courses for physicians. Now that the graduate academic year is drawing toward its end the results can be assayed with some accuracy.

The largest and longest of the courses has been that in general medicine, with twenty-five exercises conducted at various Boston hospitals from October 1 through April 8. The original registration was 220 at $50 a person, a third of the registrants not being members of the Massachusetts Medical Society. The Middlesex West course on general medicine, in Framingham, has consisted of twelve exercises between October 20 and March 23, conducted jointly with the Middlesex West District Medical Society; the Fitchburg course in general medicine has comprised five exercises held between January 7 and April 1. The enthusiasm has been such that an extra session has been requested. The courses held at the Heywood Memorial Hospital in Gardner have been a co-operative effort of staff and Institute. Plans for Springfield and Fall River are under way.

Meanwhile lists of speakers for various meetings have been drawn up, postgraduate teaching as conducted in other states has been investigated and assayed, and information about these successful ventures in Massachusetts has been given to other state societies seeking advice.

Whether or not the executive secretary of the Institute, like the Duke of Marlborough, rides in the whirlwind, like him she certainly directs the storm with courage and conviction.

1953 RED CROSS FUND

THIS month volunteer workers are energetically collecting the contributions necessary for continued operation of the American Red Cross. The funds raised go to the support of a program, year long and world wide, on behalf of thousands in need or distress. The phase of this program concerned with blood and blood derivatives should be of especial interest to physicians, who are the intermediaries between the collecting agency and the patients in need of blood and blood fractions.

Half the blood that doctors give to their patients in hospitals all over the United States is received as a result of the Red Cross blood program, and it is estimated that in the next fiscal year 60 per cent of the blood will be derived from this source (last year the Red Cross collected 1,681,000 pints of blood for civilian, military and veterans' hospitals in this country, as well as 2,439,700 pints for shipment to the armed forces in Korea). In addition, in 1952, physicians received almost 1,000,000 units (of 2 cc. each) of gamma globulin for prophylaxis of measles, hepatitis and poliomyelitis; more than 18,000 units (of 100 cc. each) of albumin for the treatment of hypoproteinemia and shock; and more than 500 units (of 2 gm. each) of fibrinogen for the treatment of uncontrolled hemorrhage in pregnancy. In the coming year the Red Cross must provide an additional 2,000,000 pints of blood, the collection and fractionation of which will cost $7,000,000 — from this extra blood gamma globulin will be extracted so that attempts to control epidemics of poliomyelitis can be extended to new areas.

In addition to the blood program, during 1951–52 (the costliest disaster year since 1937), emergency or rehabilitation assistance was given to 32,000 families in 45 states and Alaska, as well as to the 27,000 families requiring help as a result of the Kansas-Missouri-Oklahoma-Illinois flood during the summer of 1951. Other Red Cross activities included aid to troops in Korea and the United States, help to veterans in processing their claims for Government benefits, as well as volunteer service in Veterans Administration hospitals, training of more than 8500 nurse's aides, a contribution of $204,500 to the relief of suffering abroad, operation of highway first-aid stations and training of personnel engaged in employee safety programs in industry.

In responding to this appeal the physician should bear in mind the facts that the blood provided by the Red Cross is given directly to him for distribution, not to his patient, and that the expenses of the blood program (approximately $6 a pint for blood, $4 for each 10 cc. of gamma globulin, $12 for each 100 cc. of albumin and $35 for each 2 gm. of fibrinogen) depend on the voluntary contributions received during the campaign. More than token support should come from doctors, whose example will mean much to the patients who have already benefited from the Red Cross blood program or who may do so in the future. Physicians are therefore urged to give generously to the support of a program whose continuing existence is vital to the welfare of all citizens, in times of peace and war and disaster alike.

Dr. Hero was the presiding officer at the eclectic medical society meeting at Syracuse, N. Y.; an appropriate cognomen for the occasion.

Boston M. & S. J., *March 16, 1853*

MASSACHUSETTS MEDICAL SOCIETY

CHARLES READY WILLIAMSON (1916–1953)

Charles Ready Williamson was born in Auburn, Maine, on November 26, 1916, and died in Newton on January 13, 1953. He was brought up in Tennessee, where he received his early education. He graduated from the University of Virginia in 1938. He received his medical degree from Harvard Medical School in 1942, and was a member of the Boylston Medical Society, Nu Sigma Nu and the Aesculapian Club of Boston, and was elected permanent vice-president of his class. He was married to Anne Livingstone, of Newton, in 1942 and served an internship on the Harvard Service at the Boston City Hospital until 1943, when he entered service in the United States Navy. He was attending physician at Cushing and Boston Veterans Ad-

ministration hospitals, visiting physician at Faulkner Hospital and junior visiting physician at Boston City Hospital. He was chief of medicine at Brooks Hospital from 1951 until his death, and taught internal medicine as assistant in medicine at Harvard Medical School. He served as director of the Special Heart Survey of the Massachusetts Medical Society during the extensive investigations of cardiac case finding by mass x-ray screening technics with photofluorographic films. He was a member of the American Federation for Clinical Research and a fellow of the American Medical Association. He was certified by the American Board of Internal Medicine.

He spent most of his time in the Navy as medical officer aboard the destroyer *Emmons* until its sinking at Okinawa in 1945. At that time he was awarded the Bronze Star for heroism in rescuing wounded men from the sinking vessel and for his work with the survivors in the sea awaiting rescue and later aboard the rescue vessels. He received a citation for electing to remain with the wounded and continue their care rather than accept return to the United States after this. He was authorized the Navy Combat "V" and remained in the Naval Reserve after assignment to inactive duty in 1946.

He is survived by his widow and four children and by a host of devoted patients and professional associates. He was a leader in improving the practice of medicine and care of patients in his professional community. His skill, insight, intelligence and loyalty to his patients made his contribution to their welfare truly impressive. It is doubtful if any physician of his years ever did more or was so warmly loved and highly respected by his patients and his colleagues.

M. P. O.

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Boston University School of Medicine, 1942.
Paget, John Francis, 53 Worthington Road, Brookline.
Tufts College Medical School, 1940.
Parkhurst, Gerald F., 153 Oakley Road, Belmont.
University of Vermont College of Medicine, 1946.
Schier, William Davies, Jr., 176 Marlboro Street, Boston.
Harvard Medical School, 1946.
Singer, Richard Bunker, 17 Summer Street, Cohasset.
University of Pennsylvania School of Medicine, 1939.
Standish, Christopher Thomas, Moore Road, Wayland.
McGill University Faculty of Medicine, 1944.
Stefanini, Mario, 190 Scituate Street, Arlington.
University of Rome Medical School, 1939. Sponsor: Dr. Lamar Soutter, 203 Commonwealth Avenue, Boston.
Waddell, William Rhoads, 167 Walnut Street, Brookline.
Harvard Medical School, 1943.
Wentworth, Mary-Phyllis, 501 Beacon Street, Boston.
Tufts College Medical School, 1949.
White, Chester Wirt, Jr., 72 Arlington Street, Newton.
Boston University School of Medicine, 1951.
Wiseburg, Isadore, 1217 North Shore Road, Revere.
Midwest Medical College, 1934. Sponsor: Dr. G. Lynde Gately, 624 Bennington Street, East Boston.

Charles G. Shedd, M.D., *Secretary*
1180 Beacon Street, Brookline

Worcester

Carroll, Joseph Vincent, 30 Great Brook Valley, Worcester.
Georgetown University School of Medicine, 1951.
Cataldo, Felix George, City Hospital, Worcester.
Tufts College Medical School, 1947.
Courtin, Raymond Frank, 42 Westwood Drive, Worcester.
St. Thomas's Hospital Medical School, 1935. Sponsor: Dr. Bancroft C. Wheeler, 27 Elm Street, Worcester.
Fenton, John Edmund, V. A. Hospital, Rutland Heights.
Yale University School of Medicine.
Paskevich, Cyprus Joseph, 141 Copperfield Road, Worcester.
Marquette University School of Medicine, 1950.
Pond, Sidney M., 28 White Avenue, Worcester.
Cornell University Medical College, 1950.
Rice, Robert Astley, Worcester City Hospital, Worcester.
Tufts College Medical School, 1951.

Paul F. Bergin, M.D., *Secretary*
57 Cedar Street, Worcester

Worcester North

Deleo, John Stellario, Old Turnpike Road, Townsend.
Tufts College Medical School, 1951.
Gould, Aubrey V., Jr., 118 High Street, Winchendon.
Long Island College of Medicine, 1945.

Seymour I. Nathanson, M.D., *Secretary*
882 Main Street, Fitchburg

BOOK RECEIVED

The receipt of the following book is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Handwriting: A personality projection. By Frank Victor, M.D. 8°, cloth, 149 pp., with 8 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $3.75. (Publication No. 96, *American Lecture Series.*)

This new work on handwriting surveys the subject of graphology from Michon (1875) to the present. The text is divided into three chapters: background and evolution: and basic and applied graphology. There is a bibliography of 181 titles and a good index. The book should be in collections on graphology, psychology and psychiatry.

NOTICES

MONOGRAPH SERIES ON CANCER FOR THE PRACTICING PHYSICIAN

Because of the great demand on the part of physicians to have a complete set of the American Cancer Society's monograph series for the practicing physician, copies of the first three in the series distributed in 1948–1949 will be reprinted. These include the following: *The Cancer Problem* (by Dr. Shields Warren, 1948), *Cancer of the Head and Neck* (by Dr. Hayes Martin, 1949), and *The Diagnosis of Genitourinary Neoplasms* (by Dr. Victor F. Marshall, 1949.

These monographs are distributed on request without charge and should be ready for distribution to the State Divisions or or about March 15, 1953. The American Cancer Society will continue to mail monographs directly to physicians requesting them.

HELP WANTED — BLOOD DONATIONS

The National Blood Program is calling on physicians as well as their patients to help ensure that no one here at home or fighting in Korea need die for want of this vital substance.

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ANNOUNCEMENT

Dr. Joseph A. Mendez announces the removal of his offices to 1101 Beacon Street, Brookline, and 1727 Beacon Street, Waban.

CHILDREN'S CANCER RESEARCH FOUNDATION

On Monday, March 30, Dr. W. U. Gardner, professor of anatomy, Yale University School of Medicine, will speak on the subject "Hormonal Aspects of Experimental Tumorigenesis." This lecture will be delivered in the auditorium of the Jimmy Fund Building, 35 Binney Street, Boston, at 5 p.m. It is being given under the auspices of the Children's Cancer Research Foundation and the Department of Pathology, Harvard Medical School, at the Children's Hospital.

SOLDIERS' HOME STAFF MEETING

A meeting of the Combined Professional Staff of the Soldiers' Home will be held at the Quigley Memorial Hospital, Chelsea, on March 16, at 8 p.m. Franz J. Ingelfinger, M.D., associate professor of medicine, Boston University School of Medicine, will speak on the subject "Post-Gastrectomy Ulcer and Syndrome."

Refreshments will be served. All interested persons are invited to attend.

MASSACHUSETTS ACADEMY OF GENERAL PRACTICE

The spring clinical assembly of the Massachusetts Academy of General Practice will be held in Boston on Wednesday, April 15 (morning session, which will consist of a clinic on Peripheral Vascular Diseases, will be held in the lower Out-Patient Amphitheater of the Massachusetts General Hospital, and afternoon and evening sessions at the Hotel Shelton, 91 Bay State Road).

10 a.m. General Remarks. Dr. Robert R. Linton.
10:05. Varicose Veins and Varicose Ulcers. Dr. Charles V. Menendez.
10:30. Thrombophlebitis. Dr. Gordon A. Donaldson.
10:55. Questions and answers.
11. Obliterative Arterial Diseases. Dr. Edward Hamlin, Jr.
11:25. Peripheral Vascular Diseases Complicating Diabetes. Dr. Frank C. Wheelock.
11:50. Questions and answers.
12:30–1:00 p.m. Registration in Lobby, Hotel Shelton.
1. Luncheon in salon.
2:15. Convulsive Disorders. Dr. Douglas Davidson.
3:15. Shock Therapy. Dr. Leo Alexander.
4:30–5:30. Business Meeting.
5:30–7:00. Cocktails and dancing (center deck of roof).
7. Dinner. Geoffrey Harwood, professional writer, actor, lecturer and WBZ news commentator, will speak on the subject "Background to the News."

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY AND NEW ENGLAND DIABETES ASSOCIATION

A joint meeting of the New England Ophthalmological Society and the New England Diabetes Association will be held in the lower Out-Patient Amphitheater, Massachusetts General Hospital, on Wednesday, March 18, at 8:30 p.m.

Dr. Jonas S. Friedenwald, associate professor of ophthalmology, Johns Hopkins University School of Medicine, will speak on the subject "Diabetic Retinitis." The paper will be discussed by Drs. Howard F. Root and William P. Beetham.

Doctors and medical students are invited.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

A meeting of the New England Society of Physical Medicine will be held in the Veterans Administration Hospital, Boston, on Wednesday, March 18, at 8 p.m. A general discussion of the subject "The Role of the Therapist in Physical Medicine and Rehabilitation" will be presented.

Physicians, rehabilitation personnel and students are cordially invited.

AMERICAN SOCIETY OF X-RAY TECHNICIANS

The first international convention of the American Society of X-Ray Technicians will be held at the Royal York Hotel, Toronto, Canada, June 28 to July 2, in co-operation with the Canadian Society of Radiological Technicians.

AMERICAN GOITER ASSOCIATION

The annual meeting of the American Goiter Association will be held in the Drake Hotel, Chicago, on May 7, 8 and 9. The program will consist of papers and discussions dealing with goiter and other diseases of the thyroid gland.

SOCIETY MEETINGS AND CONFERENCES

MARCH 13. Gardner Postgraduate Seminar. Henry Heywood Memorial Hospital, Gardner. 6:00–8:00 p.m.
MARCH 13. New England Center Hospital House Officers' Association. Page 395, issue of February 26.
MARCH 13-27. Combined Anesthesia Teaching Conferences of Boston. Page 210, issue of January 29.
MARCH 13-30. Springfield Hospital Educational Program. Page 396, issue of February 26.
MARCH 13–27. Consultation Clinics for Crippled Children in Massachusetts. Page 353, issue of February 19.
MARCH 16. Soldiers' Home Staff Meeting. Notice above.
MARCH 16–APRIL 20. Hartford Medical Society. Page 42, issue of January 1.
MARCH 16-MAY 4. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.
MARCH 17. Boston Evening Clinic. Page 395, issue of February 26.
MARCH 17. South End Medical Club. Page 307, issue of February 12.
MARCH 18. New England Society of Physical Medicine. Notice above.
MARCH 18. New England Ophthalmological Society and New England Diabetes Association. Notice above.
MARCH 18–APRIL 8. Postgraduate Medical Institute, Boston. Page 452, issue of September 18.
MARCH 23. Postgraduate Course in General Medicine. Cushing Veterans Administration Hospital, Framingham. Page 697, issue of October 30.
MARCH 25. Cutter Lecture. Page 307, issue of February 12.
MARCH 25. Graduate Club of Boston, Phi Delta Epsilon Medical Fraternity. Page 307, issue of February 12.
MARCH 30. Children's Cancer Research Foundation. Notice above.
APRIL 1. Postgraduate Medical Institute Course in General Medicine. Burbank Hospital, Fitchburg. Page 1049, issue of December 25.
APRIL 4. Problems in Hematology. Drs. William B. Castle and Frank Gardner. Mount Auburn Hospital, Cambridge. 10:05 a.m.
APRIL 10. New England Society of Anesthesiologists. Page 395, issue of February 26.
APRIL 10–12. American Association of the History of Medicine. Page 308, issue of February 12.
APRIL 15. Massachusetts Academy of General Practice. Notice above.
APRIL 16–18. Boston Lying-in Hospital Postgraduate Course in Obstetrics and Pediatrics. Page 307, issue of February 12.
APRIL 19–24. National Industrial Health Conference. Page 308, issue of February 12.
APRIL 25. Alumni Association of the State University College of Medicine at New York City. Page 396, issue of February 26.
APRIL 25. Graduate Club of Boston, Phi Delta Epsilon Medical Fraternity. Page 307, issue of February 12.
APRIL 29 AND OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.
MAY 7–9. American Goiter Association. Notice above.
MAY 19–21. Massachusetts Medical Society. Hotel Statler, Boston.
MAY 25–31. First World Congress on Fertility and Sterility. Page 1001, issue of December 18.
JUNE 7–9. American College of Cardiology. Page 395, issue of February 26.
JUNE 28–JULY 2. American Society of X-Ray Technicians. Notice above.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

MAY 13. Andover Country Club, Shawsheen.

MIDDLESEX WEST

MARCH 23. Postgraduate Course in General Medicine. Cushing Veterans Administration Hospital, Framingham.

NORFOLK

MARCH 24.

WORCESTER

MAY 6. Annual Meeting. Sheraton Hotel. Dr. Louis H. Bauer, President, American Medical Association.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MARCH 19

THURSDAY, MARCH 19

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

(Notices concluded on page xv)

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LOCUM TENENS for general practice, 20 miles south of Boston for May, June and July, 1953, or any part thereof. Terms arranged. Office in home. Housekeeper and nurse to assist. Address A174, *New Eng. J. Med.* 4-tf

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BOARD-QUALIFIED INTERNIST available as fill-in or associate for period of 6 months or less. Address A204, *New Eng. J. Med.* 11-1t

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(*Additional advertisements on page xiv*)

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NOTICES (*Concluded from page 480*)

*12:00 m.–1:00 p.m. The Artificial Kidney in Shock. Dr. Carl W. Walters. Stearns Auditorium, New England Center Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, MARCH 20

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Dr. George W. Thorn and Dr. Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
*10:30 a.m.–1:30 p.m. Combined Medical and Surgical Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.
*7:00–9:00 p.m. Combined Anesthesia Teaching Conference of Boston. Amphitheater, Evans Memorial, Massachusetts Memorial Hospitals, Eighth Floor, 65 East Newton Street.

SATURDAY, MARCH 21

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, MARCH 23

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Hematology Conference. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*2:00–8:30 p.m. Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital, Waltham.
*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

TUESDAY, MARCH 24

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
11:00 a.m.–12:00 m. Regular Grand Rounds of the Pediatric Department. Dowling Amphitheater, Boston City Hospital.
*12:00 m.–1:00 p.m. Tumor Clinic. Pratt Diagnostic Clinic. New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, MARCH 25

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Medical Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.
*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Neuropathology Conference. Drs. Adams and MacMahon. Stearns Auditorium, New England Center Hospital.
*7:30 p.m. Lahey Clinic Lecture. Peripheral Vascular Disease. Drs. James A. Evans, Carl C. Bartels, James L. Poppen and David P. Boyd. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.

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Mar. 12, 1953

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